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(71) Applicant *(for all designated States except US)*: **SANTARUS, INC.** [US/US]; 10590 West Ocean Air Drive, Suite 200, San Diego, CA 92130 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HALL, Warren** [US/US]; 12929 Via Esperia, San Diego, CA (US). **OLMSTEAD, Kay** [KR/US]; 7423 Park Village Road, San Diego, CA (US). **PROEHL, Gerald, T.** [US/US]; 10590 West Ocean Air Drive, Suite 200, San Diego, CA (US).

(74) Agents: **HADDACH, Aubrey** et al.; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94306-1050 (US).

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(54) Title: COMBINATION OF PROTON PUMP INHIBITOR AND SLEEP AID

(57) Abstract: Pharmaceutical compositions comprising a proton pump inhibitor, one or more buffering agent and a sleep aid are described. Methods are described for treating gastric acid related disorders and inducing sleep, using pharmaceutical compositions comprising a proton pump inhibitor, a buffering agent, and a sleep aid.

COMBINATION OF PROTON PUMP INHIBITOR AND SLEEP AID

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/517,743 filed November 5, 2003, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention is related to pharmaceutical compositions comprising a proton pump inhibitor, a buffering agent, and a sleep aid. Methods for manufacture of the pharmaceutical compositions and use of the pharmaceutical compositions in treating disease are disclosed.

BACKGROUND OF THE INVENTION

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are a class of acid-labile pharmaceutical compounds that block gastric acid secretion pathways. Exemplary proton pump inhibitors include, omeprazole (Prilosec®), lansoprazole (Prevacid®), esomeprazole (Nexium®), rabeprazole (Aciphex®), pantoprazole (Protonix®), pariprazole, tentaprazole, and leminoprazole. The drugs of this class suppress gastrointestinal acid secretion by the specific inhibition of the H^+/K^+-ATPase enzyme system (proton pump) at the secretory surface of the gastrointestinal parietal cell. Most proton pump inhibitors are susceptible to acid degradation and, as such, are rapidly destroyed in an acidic pH environment in the stomach. Therefore, proton pump inhibitors are often administered as enteric-coated dosage forms in order to permit release of the drug in the duodenum after having passed through the stomach. If the enteric-coating of these formulated products is disrupted (*e.g.*, during trituration to compound a liquid dosage form, or by chewing an enteri-coated granular capsule or tablet), or if a co-administered buffering agent fails to sufficiently neutralize the gastrointestinal pH, the uncoated drug is exposed to stomach acid and may be degraded.

Omeprazole, a substituted bicyclic aryl-imidazole, 5-methoxy-2-[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole, is a proton pump inhibitor that inhibits gastrointestinal acid secretion. U.S. Patent No. 4,786,505 to Lovgren *et al.* teaches that a pharmaceutical oral solid dosage form of omeprazole must be protected from contact with acidic gastrointestinal juice by an enteric-coating to maintain its pharmaceutical activity and describes an enteric-coated omeprazole preparation containing one or more subcoats

between the core material and the enteric-coating. Non-enteric coated pharmaceutical compositions have also been described, which facilitate immediate release of the pharmaceutically active ingredient into the stomach and permit stomach uptake of pharmaceutical agents. Use of non-enteric-coated compositions involves the administration of one or more buffering agents with an acid labile proton pump inhibitor. The buffering agent is thought to prevent substantial degradation of the acid labile pharmaceutical agent in the acidic environment of the stomach by raising the stomach pH. See, *e.g.*, U.S. Patent Nos. 5,840,737 and 6,489,346.

Proton pump inhibitors are typically prescribed for short-term treatment of active duodenal ulcers, gastrointestinal ulcers, gastro esophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. These above-listed conditions commonly arise in healthy or critically ill patients of all ages, and may be accompanied by significant upper gastrointestinal bleeding.

It is believed that omeprazole, lansoprazole and other proton pump inhibiting agents reduce gastrointestinal acid production by inhibiting H^+/K^+-ATPase of the parietal cell, which is the final common pathway for gastrointestinal acid secretion. See, *e.g.*, Fellenius *et al.*, Substituted Benzimidazoles Inhibit Gastrointestinal Acid Secretion by Blocking H^+/K^+-ATPase, *Nature*, 290: 159-161 (1981); Wallmark *et al.*, The Relationship Between Gastrointestinal Acid Secretion and Gastrointestinal H^+/K^+-ATPase Activity, *J. Biol. Chem.*, 260: 13681-13684 (1985); and Fryklund *et al.*, Function and Structure of Parietal Cells After H^+/K^+-ATPase Blockade, *Am. J. Physiol.*, 254 (1988).

Proton pump inhibitors have the ability to act as weak bases which reach parietal cells from the blood and diffuse into the secretory canaliculi. There the drugs become protonated and thereby trapped. The protonated compound can then rearrange to form a sulfenamide which can covalently interact with sulfhydryl groups at critical sites in the extra cellular (luminal) domain of the membrane-spanning H^+/K^+-ATPase. See, *e.g.*, Hardman *et al.*, *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 907 (9th ed. 1996). As such, proton pump inhibitors are prodrugs that must be activated within parietal cells to be effective. The specificity of the effects of proton pump inhibiting agents is also dependent upon: (a) the selective distribution of H^+/K^+-ATPase; (b) the requirement for acidic conditions to catalyze generation of the reactive inhibitor; and (c) the trapping of the protonated drug and the cationic sulfenamide within the acidic canaliculi and adjacent to the target enzyme.

Sleep Aids

Sleeplessness is a common complaint. Numerous pharmaceutical agents have been developed to induce relaxation, sedation, and/or sleep. Pharmaceutical agents that induce sleep are generally known as "hypnotics." Other sleep aids facilitate sleep by having a relaxing or sedative effect. Hypnotics include benzodiazepine hypnotics, non-benzodiazepine hypnotic, antihistamine hypnotics, barbiturates, peptide hypnotics, and herbal extracts. Hypnotics are further classified as fast-acting, intermediate-acting, and long-acting. Fast-acting hypnotics (also called short-acting hypnotics) allow a subject to quickley go to sleep or return to sleep (to complete a sleep period), and are therefore useful for treating sleep disorders associated with difficulty falling asleep or returning to sleep such as sleep onset insomnia. Intermediate-acting hypnotics induce sleep maintenance, and are therefore useful for treating an inability to stay asleep. Long-acting hypnotics induce sleep by preventing early morning awakening that interrupts the completion of a full sleep period, *e.g.*, as seen in sleep offset insomnia. Herbal extracts of valerian, chamomile, lavender oil, hops, and/or passion-flower, may act as sleep-inducing hypnotics, or may facilitate sleep by inducing relaxation. Peptide hypnotics include gabapeptin, as described in U.S. Patent No. 6,372,792. Peptide hormones useful as sleep aids incude melatonin. The amino acid tryptophan is known to have a sedative effect. Sleep aids can be formulated for a defined release profile such as controlled release or pulsed release, *e.g.*, as described in U.S. Patent No. 6,485,792, to control the rate of release of a hypnotic following administration to a patient.

SUMMARY OF THE INVENTION

Pharmaceutical compositions including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one sleep aid, are provided herein. Methods are provided for treating gastric acid related disorders and inducing sleep, using pharmaceutical composition of the present invention.

Proton pump inhibitors include, but are not limited to, omeprazole, hydroxyomeprazole, esomeprazole, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, periprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof. In one embodiment, the proton pump inhibitor is omeprazole or a free base,

free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof. Compositions can contain between about 5 mgs to about 200 mgs of proton pump inhibitor, specifically about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mgs, or about 60 mgs of the proton pump inhibitor.

Compositions are provided such that an initial serum concentration of the proton pump inhibitor is greater than about 0.1 μg/ml at any time within about 30 minutes after administering the formulation. Initial serum concentration of the proton pump inhibitor can be greater than about 0.5 μg/ml at any time within about 1 hour after administration, greater than about 0.3 μg/ml at any time within about 45 minutes after administration, or greater than about 0.1 μg/ml is maintained from at least about 30 minutes to about 1 hour after administration of the composition.

Compositions are provided such that a serum concentration of proton pump inhibitor greater than about 0.1 μg/ml can be maintained from at least about 15 minutes to about 30 minutes. A serum concentration of greater than about 0.1 μg/ml can be maintained from at least about 30 minutes to about 45 minutes. A serum concentration of greater than about 0.25 μg/ml can be maintained from at least about 30 minutes to about 1 hour. A serum concentration of greater than about 0.25 μg/ml can be maintained from at least about 30 minutes to about 45 minutes. A serum concentration of greater than about 0.25 μg/ml can be maintained from at least about 15 minutes to about 30 minutes.

Compositions of the invention can be administered in an amount to maintain a serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml from about 15 minutes to about 1 hour after administration. Compositions of the invention can be administered in an amount to maintain a serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml from about 15 minutes to about 1.5 hours after administration. Compositions of the invention can be administered in an amount to maintain a serum concentration of the proton pump inhibitor greater than about 0.1 μg/ml from about 15 minutes to about 1.5 hours after administration. Compositions of the invention can be administered in an amount to achieve an initial serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml at any time from about 5 mintues to about 30 minutes after administration. Compositions of the invention can be administered in an amount to maintain a serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml from about 15 minutes to about 30 minutes after administration. Compositions of the invention can be administered in an amount to achieve an initial serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml at any time within about 30 minutes

after administration. Compositions of the invention can be administered in an amount to achieve an initial serum concentration of the proton pump inhibitor greater than about 0.1 μg/ml at any time within about 15 minutes after administration. Compositions of the invention can be administered in an amount to achieve an initial serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml at any time within about 15 minutes after administration.

Compositions are provided wherein, upon oral administration to the subject, the composition provides a pharmacokinetic profile such that at least about 50% of total area under serum concentration time curve (AUC) for the proton pump inhibitor occurs within about 2 hours after administration of a single dose of the composition to the subject. Compositions are provided wherein, upon oral administration to the subject, the area under the serum concentration time curve (AUC) for the proton pump inhibitor in the first 2 hours is at least about 60% of the total area. Compositions are provided wherein the area under the serum concentration time curve (AUC) for the proton pump inhibitor in the first 2 hours is at least about 70% of the total area.

Compositions are provided wherein the at least about 50% of total area under the serum concentration time curve (AUC) for the proton pump inhibitor occurs within about 1.75 hours after administration of a single dose of the composition to the subject. Compositions are provided wherein the at least about 50% of total area under the serum concentration time curve (AUC) for the proton pump inhibitor occurs within about 1.5 hours after administration of a single dose of the composition to the subject. Compositions are provided wherein the at least about 50% of total area under the serum concentration time curve (AUC) for the proton pump inhibitor occurs within about 1 hour after administration of a single dose of the composition to the subject.

Compositions are provided wherein, upon oral administration to the subject, the composition provides a pharmacokinetic profile such that the proton pump inhibitor reaches a maximum serum concentration within about 1 hour after administration of a single dose of the composition. Compositions are provided wherein the maximum serum concentration is reached within about 45 minutes after administration of the composition. Compositions are provided wherein the maximum serum concentration is reached within about 30 minutes after administration of the composition. Compositions are provided wherein the maximum serum concentration is at least about 0.25 μg proton pump inhibitor/ml. Compositions are provided wherein the maximum serum concentration is at least about 0.5 μg proton pump inhibitor/ml.

Compositions are provided wherein the proton pump inhibitor is microencapsulated with a material that enhances the shelf-life of the pharmaceutical composition. The material that enhances the shelf-life of the pharmaceutical composition includes, but is not limited to, cellulose hydroxypropyl ethers, low-substituted hydroxypropyl ethers, cellulose hydroxypropyl methyl ethers, methylcellulose polymers, ethylcelluloses and mixtures thereof, polyvinyl alcohol, hydroxyethylcelluloses, carboxymethylcelluloses, salts of carboxymethylcelluloses, polyvinyl alcohol, polyethylene glycol co-polymers, monoglycerides, triglycerides, polyethylene glycols, modified food starch, acrylic polymers, mixtures of acrylic polymers with cellulose ethers, cellulose acetate phthalate, sepifilms, cyclodextrins; and mixtures thereof. The cellulose hydroxypropyl ether can be, but is not limited to, Klucel®, Nisswo HPC or PrimaFlo HP22. The cellulose hydroxypropyl methyl ether can be, but is not limited to, Seppifilm-LC, Pharmacoat®, Metolose SR, Opadry YS, PrimaFlo, MP3295A, BenecelMP824, or BenecelMP843. The mixture of methylcellulose and hydroxypropyl and methylcellulose polymers can be, but is not limited to, Methocel®, Benecel-MC, or Metolose®. The ethylcellulose or mixture thereof can be, but is not limited to, Ethocel®, BenecelMO43, Celacal, Cumibak NC, and E461. The polyvinyl alcohol can be, but is not limited to, Opadry AMB. Composition can include a mixture wherein the hydroxyethylcellulose is Natrosol®, the carboxymethylcellulose is Aqualon®-CMC, the polyvinyl alcohol and polyethylene glycol co-polymer is Kollicoat IR®, and the acrylic polymers are selected from Eudragits® EPO, Eudragits® RD100, and Eudragits® E100. The material that enhances the shelf-life of the pharmaceutical composition can further include an antioxidant, a plasticizer, a buffering agent, or mixtures thereof.

Compositions are provided that include (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, wherein at least some of the proton pump inhibitor is coated, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one sleep aid, wherein the sleep aid may be coated. Suitable coatings include, but are not limited to, gastric resistant coatings such as enteric coatings, controlled-release coatings, enzymatic-controlled coatings, film coatings, sustained-release coatings, immediate-release coatings, and delayed-release coatings.

Compositions including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton

pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one sleep aid are provided, wherein the buffering agent is an alkaline metal salt or a Group IA metal selected from a bicarbonate salt of a Group IA metal, a carbonate salt of a Group IA metal. The buffering agent can be, but is not limited to, an amino acid, an acid salt of an amino acid, an alkali salt of an amino acid, aluminum hydroxide, aluminum hydroxide/magnesium carbonate/calcium carbonate co-precipitate, aluminum magnesium hydroxide, aluminum hydroxide/magnesium hydroxide co-precipitate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, calcium acetate, calcium bicarbonate, calcium borate, calcium carbonate, calcium citrate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium lactate, calcium phthalate, calcium phosphate, calcium succinate, calcium tartrate, dibasic sodium phosphate, dipotassium hydrogen phosphate, dipotassium phosphate, disodium hydrogen phosphate, disodium succinate, dry aluminum hydroxide gel, L-arginine, magnesium acetate, magnesium aluminate, magnesium borate, magnesium bicarbonate, magnesium carbonate, magnesium citrate, magnesium gluconate, magnesium hydroxide, magnesium lactate, magnesium metasilicate aluminate, magnesium oxide, magnesium phthalate, magnesium phosphate, magnesium silicate, magnesium succinate, magnesium tartrate, potassium acetate, potassium carbonate, potassium bicarbonate, potassium borate, potassium citrate, potassium metaphosphate, potassium phthalate, potassium phosphate, potassium polyphosphate, potassium pyrophosphate, potassium succinate, potassium tartrate, sodium acetate, sodium bicarbonate, sodium borate, sodium carbonate, sodium citrate, sodium gluconate, sodium hydrogen phosphate, sodium hydroxide, sodium lactate, sodium phthalate, sodium phosphate, sodium polyphosphate, sodium pyrophosphate, sodium sesquicarbonate, sodium succinate, sodium tartrate, sodium tripolyphosphate, synthetic hydrotalcite, tetrapotassium pyrophosphate, tetrasodium pyrophosphate, tripotassium phosphate, trisodium phosphate, trometamol, and mixtures thereof. In particular, the buffering agent can be sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium oxide, magnesium hydroxide, magnesium carbonate, aluminum hydroxide, and mixtures thereof.

Compositions are provided as described herein, including sodium bicarbonate is present in about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg proton pump inhibitor. Compositions are provided as described herein, wherein the buffering agent is a mixture of sodium bicarbonate and magnesium hydroxide, and each buffering agent is present in about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg proton pump inhibitor. Compositions are provided as described herein, wherein the buffering agent is a

mixture of sodium bicarbonate, calcium carbonate, and magnesium hydroxide, and each buffering agent is present in about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg of the proton pump inhibitor.

Compositions are provided as described herein, wherein the buffering agent is present in an amount of about 0.1 mEq/mg to about 5 mEq/mg of the proton pump inhibitor, or about 0.5 mEq/mg to about 3 mEq/mg of the proton pump inhibitor, or about 0.8 mEq/mg to about 2.5 mEq/mg of the proton pump inhibitor, or about 0.9 mEq/mg to about 2.0 mEq/mg of the proton pump inhibitor, or about 0.9 mEq/mg to about 1.8 mEq/mg of the proton pump inhibitor. Compositions are provided as described herein, wherein the buffering agent is present in an amount of at least 1.0 mEq/mg to about 1.5 mEq/mg of the proton pump inhibitor, or at least 0.5 mEq/mg of the proton pump inhibitor. Compositions are provided as described herein, including about 200 to 3000 mg of buffering agent, or about 500 to about 2500 mg of buffering agent, or about 1000 to about 2000 mg of buffering agent, or about 1500 to about 2000 mg of buffering agent.

Compositions are provided as described herein, where the buffering agent to proton pump inhibitor ratio is at least 10:1; at least 12:1; at least 15:1; at least 20:1; at least 22:1; at least 25:1; at least 30:1; at least 35:1; and at least 40:1.

Compositions including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one sleep aid are provided, wherein the sleep aid is a hypnotic. The hypnotic can be, but is not limited to, fast-acting, intermediate-acting, or long-acting. The hypnotic can be, but is not limited to, a benzodiazepine hypnotic, non-benzodiazepine hypnotic, antihistamine hypnotic, antidepressant hypnotic, herbal extract, barbiturate, or peptide hypnotic. The hypnotic can be a benzodiazepine hypnotic including, but not limited to, a fast-acting benzodiazepine, an intermediate-acting benzodiazepine, or a long-acting benzodiazepine. The hypnotic can be a fast-acting benzodiazepine including, but not limited to, triazolam, brotizolam, loprazolam, lormetazepam, flunitrazepam, flurazepam, nitrazepam, or quazepam. The hypnotic can be an intermediate-acting benzodiazepine including, but not limited to, estazolam, temazepam, lorazepam, oxazepam, diazepam, halazepam, and prazepam. The hypnotic can be a long-acting benzodiazepine including, but not limited to, alprazolam, chlordiazepoxide, or clorazepate.

Compositions are provided as described herein, wherein the hypnotic is a non-benzodiazepine hypnotic. The non-benzodiazepine hypnotic can be, but is not limited to, an imidazopyridine or pyrazolopyrimidine hypnotic. An imidazopyridine hypnotic can be, but is not limited to, zolpidem or zolpidem tartarate. A pyrazolopyrimidine hypnotic can be, but is not limited to, zopiclone, eszopiclone, or zaleplon. The non-benzodiazepine hypnotic can be indiplone.

Compositions are provided as described herein, wherein the hypnotic is an antihistamine hypnotic including, but is not limited to, diphenhydramine, doxylamine, phenyltoloxamine, or pyrilamine. Compositions are provided as described herein, wherein the hypnotic is an antidepressant hypnotic including, but not limited to, doxepin, amtriptyline, trimipramine, trazodon, nefazodone, buproprion, or bupramityiptyline. Compositions are provided as described herein, wherein the hypnotic is an herbal extract including, but not limited to valerian extract or amentoflavone. Compositions are provided as described herein, wherein the hypnotic is a hormone including, but not limited to, melatonin. Compositions are provided as described herein, wherein the hypnotic is a peptide hypnotic including, but not limited to, gabapeptin. Compositions are provided as described herein, wherein the hypnotic is formulated for controlled release. Compositions are provided as described herein, wherein the hypnotic is formulated for pulsed release.

Compositions including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one sleep aid are provided, wherein the composition is in a dosage form selected from a powder, a tablet, a bite-disintegration tablet, a chewable tablet, a capsule, an effervescent powder, a rapid-disintegration tablet, or an aqueous suspension produced from powder.

Compositions are provided as described herein, further including one or more excipients including, but not limited to, parietal cell activators, erosion facilitators, flavoring agents, sweetening agents, diffusion facilitators, antioxidants and carrier materials selected from binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, anti-adherents, and antifoaming agents.

Methods are provided for treating a gastric acid related disorder and inducing sleep in a subject by administering to the subject a pharmaceutical composition including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least

one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid; and (c) a therapeutically effective amount of at least one sleep aid, wherein the proton pump inhibitor treats the gastric acid related disorder and the sleep aid induces sleep in the subject. Methods are provided wherein the composition as described herein is formulated for stomach delivery of the proton pump inhibitor. Methods are provided wherein the composition as described herein is formulated for duodenal delivery of some of the proton pump inhibitor.

Methods are provided for treating a gastric acid related disorder including, but not limited to duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison syndrome, heartburn, esophageal disorder, and acid dyspepsia. Method are provided wherein the proton pump inhibitor treats an episode of gastric acid related disorder. Methods are provided wherein the proton pump inhibitor prevents or treats the gastric acid related disorder when the subject is asleep. Methods are provided wherein the proton pump inhibitor prevents or treats the gastric acid related disorder when the subject is asleep, further wherein at least some of the proton pump inhibitor is coated, optionally enteric-coated.

Methods are provided for administering to the subject a pharmaceutical composition including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid; and (c) a therapeutically effective amount of at least one sleep aid, the proton pump inhibitor treats the gastric acid related disorder and the sleep aid induces sleep in a subject suffering from sleeplessness or insomnia. Methods are provided wherein the insomnia includes, but is not limited to, sleep onset insomnia, sleep maintenance insomnia, or sleep offset insomnia. Methods are provided wherein the sleep aid induces sleep onset in a subject suffering from sleep onset insomnia. Methods are provided wherein the composition is administered to a subject suffering from sleep onset insomnia before the subject retires, wherein the sleep aid is a fast-acting hypnotic. Methods are provided wherein the sleep aid induces sleep maintenance in a subject suffering from sleep maintenance insomnia, and the proton pump inhibitor prevents or treats the gastric acid related disorder when the subject is asleep. Methods are provided wherein the sleep aid induces sleep maintenance in a subject suffering from sleep maintenance insomnia, wherein the sleep aid is an intermediate-acting hypnotic. Methods are provided wherein the sleep aid is an intermediate-acting hypnotic that

prevents awakening in a subject suffering from sleep offset insomnia. Methods are provided wherein the sleep aid is an intermediate-acting hypnotic that prevents awakening in a subject suffering from sleep offset insomnia, wherein the proton pump inhibitor prevents or treats the gastric acid related disorder when the subject is asleep. Methods are provided wherein the sleep aid prevents awakening in a subject suffering from sleep offset insomnia, wherein the sleep aid is a long-acting hypnotic. Methods are provided wherein the sleep aid induces sleep in a subject after the subject is awakened by distress associated with the gastric acid related disorder.

Methods are provided for treating a gastric acid related disorder and inducing sleep in a subject by administering to the subject a pharmaceutical composition including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid; and (c) a therapeutically effective amount of at least one sleep aid, wherein the proton pump inhibitor treats the gastric acid related disorder and the sleep aid induces sleep in the subject, wherein the composition wherein is in dosage form including, but not limited to, a powder, a tablet, a bite-disintegration tablet, a chewable tablet, a capsule, an effervescent powder, a rapid-disintegration tablet, or an aqueous suspension produced from powder. Methods are provided wherein the composition further comprises one or more excipients including, but not limited to, parietal cell activators, erosion facilitators, flavoring agents, sweetening agents, diffusion facilitators, antioxidants and carrier materials selected from binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, anti-adherents, and antifoaming agents.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to pharmaceutical compositions comprising a proton pump inhibior, a buffering agent, and a sleep aid, wherein the compositions are useful for the treatment of a disease, condition or disorder. Methods of treatment using the pharmaceutical compositions of the present invention are also described.

It has been discovered that pharmaceutical compositions comprising (1) an acid labile proton pump inhibitor together with (2) one or more buffering agents and (3) a sleep aid, provide relief from gastric acid related disorders and treat sleeplessness by inducing sleep. It has been discovered that pharmaceutical compositions comprising (1) an acid labile proton pump inhibitor which is microencapsulated with a material that enhances the shelf-life of the

pharmaceutical composition, together with (2) one or more buffering agents, and (3) a sleep aid, provide relief from gastric acid related disorders and treat sleeplessness by inducing sleep and further provide superior performance by enhancing shelf-life stability of the pharmaceutical composition during manufacturing and storage.

GLOSSARY

To more readily facilitate an understanding of the invention and its preferred embodiments, the meanings of terms used herein will become apparent from the context of this specification in view of common usage of various terms and the explicit definitions of other terms provided in the glossary below or in the ensuing description.

As used herein, the terms "comprising," "including," and "such as" are used in their open, and non-limiting sense.

The term "about" is used synonymously with the term "approximately." Illustratively, the use of the term "about" indicates that values slightly outside the cited values, i.e., plus or minus 0.1% to 20%, which are also effective and safe. Such dosages are thus encompassed by the scope of the claims reciting the terms "about" and "approximately."

The phrase "acid-labile pharmaceutical agent" refers to any pharmacologically active drug subject to acid catalyzed degradation.

"Anti-adherents," "glidants," or "anti-adhesion" agents prevent components of the formulation from aggregating or sticking and improve flow characteristics of a material. Such compounds include, *e.g.*, colloidal silicon dioxide such as Cab-o-sil®; tribasic calcium phosphate, talc, corn starch, DL-leucine, sodium lauryl sulfate, magnesium stearate, calcium stearate, sodium stearate, kaolin, and micronized amorphous silicon dioxide (Syloid®)and the like.

The term "antidepressant hypnotic" refers to an agent that can be used as hypnotic, usually in an amount that is sufficient to have sleep-inducing (hypnotic) effect, and lower than the amount necessary to antidepressant effect.

"Antifoaming agents" reduce foaming during processing which can result in coagulation of aqueous dispersions, bubbles in the finished film, or generally impair processing. Exemplary anti-foaming agents include silicon emulsions or sorbitan sesquoleate.

"Antihistamine hypnotic" refers to those antihistamines (histamine receptor H1 antagonists) that induce sleep; an alternate term is "sedating antihistamine." Examples of antihistamine hypnotics include but are not limited to diphenhydramine (Benadryl), hydroxyzine (Atarax), doxylamine, phenyltoloxamine, or pyrilamine.

"Antioxidants" include, *e.g.*, butylated hydroxytoluene (BHT), sodium ascorbate, and tocopherol.

The term "barbiturate" refers to a class of sleeping aids. Examples of barbiturate include but are not limited to pentobarbital (Nembutal) and secobarbital (Seconal).

The term "benzodiazepine hypnotics" refers to a class of hypnotics that are have a similar chemical structure and act selectively on the polysynaptic pathways throughout the central nervous system. Approximately 2000 benzodiazepines have been synthesized. Benzodiazepine receptor sites have been identified in the brain. Without being limited by this theory, the mechanism of benzodiazepine action may be related to the metabolism of gamma aminobutyric acid (GABA). Benzodiazepine hypnotics are often classified, based on their mode of action, in one or more of three classes: fast-acting, intermediate-acting, and long-acting. Some benzodiazepine hypnotics are assigned to more than one class. Fast-acting benzodiazepine hypnotics that induce sleep quickly may be appropriate to treat sleeplessness or sleep onset insomnia (initial insomnia). Intermediate-acting benzodiazepine hypnotics help a subject remain asleep, and may be appropriate for problems related to frequent awakening, *e.g.*, to treat sleep maintenance insomnia. Long-acting benzodiazepine hypnotics help a subject remain asleep for an extended period, and may be appropriate for problems related to awakening before a fully restorative sleep period is complete, *e.g.*, to treat sleep offset insomnia or early morning awakening. Benzodiazepine hypnotics include drugs such as diazepam (Valium®), chlordiazepoxide (Librium®), oxazepam (Serax®), lorazepam (Ativan®), alprazolam (Xanax®), clonazepam (Clonopin®), and others. Some, such as flurazepam (Dalmane®), alprazolam (Xanax®) and triazolam (Halcion®).

"Binders" impart cohesive qualities and include, *e.g.*, alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (*e.g.*, Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (*e.g.*, Klucel®), ethylcellulose (*e.g.*, Ethocel®), and microcrystalline cellulose (*e.g.*, Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crospovidone; povidone; polymethacrylates such as Eugradit® NE30D and RS30D; hydroxypropylmethylcellulose; hydroxypropylcellulose; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose, glucose, dextrose, molasses, mannitol, sorbitol, xylitol, and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (*e.g.*, Polyvidone® CL, Polyvidone®, Kollidon® CL, Polyplasdone® XL,

Polyplasdone® XL-10), and larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, water, alcohol, and the like.

"Bioavailability" refers to the extent to which an active moiety, *e.g.*, drug or metabolite is absorbed into the general circulation and becomes available at the site of drug action in the body.

"Carrier materials" include any commonly used excipients in pharmaceutics and should be selected on the basis of compatibility with the proton pump inhibitor and the release profile properties of the desired dosage form. Exemplary carrier materials include, *e.g.*, binders, suspending agents, disintegration agents, filing agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. "Pharmaceutically compatible carrier materials" may comprise, *e.g.*, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, *e.g.*, *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

"Character notes" include, *e.g.*, aromatics, basis tastes, and feeling factors. The intensity of the character note can be scaled from 0-none, 1-slight, 2-moderate, or 3-strong.

A "derivative" is a compound that is produced from another compound of similar structure by the replacement of substitution of an atom, molecule or group by another suitable atom, molecule or group. For example, one or more hydrogen atom of a compound may be substituted by one or more alkyl, acyl, amino, hydroxyl, halo, haloalkyl, aryl, heteroaryl, cycloaolkyl, heterocycloalkyl, or heteroalkyl group to produce a derivative of that compound.

"Diffusion facilitators" and "dispersing agents" include materials that control the diffusion of an aqueous fluid through a coating. Exemplary diffusion facilitators/dispersing agents include, *e.g.*, hydrophilic polymers, electrolytes, proteins, peptides, and amino acids, Tween ® 60 or 80, PEG and the like. Combinations of one or more erosion facilitator with one or more diffusion facilitator can also be used in the present invention.

"Diluents" increase bulk of the composition to facilitate compression. Such compounds include *e.g.*, lactose; starch; mannitol; sorbitol; dextrose; microcrystalline

cellulose such as Avicel®; dibasic calcium phosphate; dicalcium phosphate dihydrate; tricalcium phosphate; calcium phosphate; anhydrous lactose; spray-dried lactose; pregelatinzed starch; compressible sugar, such as Di-Pac® (Amstar); mannitol; hydroxypropylmethylsellulose; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; powdered cellulose; calcium carbonate; glycine; kaolin; mannitol; sodium chloride; inositol; bentonite; and the like.

The term "disintegrate" includes both the dissolution and dispersion of the dosage form when contacted with gastrointestinal fluid.

"Disintegration agents" facilitate the breakup or disintegration of a substance. Examples of disintegration agents include a starch, *e.g.*, a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®; a cellulose such as a wood product, methylcrystalline cellulose, *e.g.*, Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, sodium carboxymethylcellulose, croscarmellose, or a carboxymethylcellulose such as Primogel® and Explotab®; a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose; a cross-linked starch such as sodium starch glycolate; a cross-linked polymer such as crospovidone; a cross-linked polyvinylpyrrolidone; a calcium; alginate such as alginic acid or a salt of alginic acid such as sodium alginate; a clay such as Veegum® HV (magnesium aluminum silicate); a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth; sodium starch glycolate; bentonite; a natural sponge; a surfactant; a resin such as a cation-exchange resin; citrus pulp; sodium lauryl sulfate; sodium lauryl sulfate in combination starch; and the like.

"Drug absorption" or "absorption" refers to the process of movement from the site of administration of a drug toward the systemic circulation, *e.g.*, into the bloodstream of a subject.

"Erosion facilitators" include materials that control the erosion of a particular material in gastrointestinal fluid. Erosion facilitators are generally known to those of ordinary skill in the art. Exemplary erosion facilitators include, *e.g.*, hydrophilic polymers, electrolytes, proteins, peptides, and amino acids.

"Filling agents" include compounds such as lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose

powder, dextrose; dextrates; dextran, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

"Flavoring agents" or "sweeteners" useful in the pharmaceutical compositions of the present invention include, *e.g.*, acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sylitol, sucralose, sorbitol, Swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, *e.g.*, anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof.

"Gastrointestinal fluid" is the fluid of stomach secretions of a subject or the saliva of a subject after oral administration of a composition of the present invention, or the equivalent thereof. An "equivalent of stomach secretion" includes, *e.g.*, an in vitro fluid having similar content and/or pH as stomach secretions such as a 1% sodium dodecyl sulfate solution or 0.1N HCl solution in water.

"Half-life" refers to the time required for the plasma drug concentration or the amount in the body to decrease by 50% from its maximum concentration.

The term "hypnotic" refers to an agent that induces sleep or that causes an insensitivity to pain which prevents or disrupts sleep. Hypnotics include sedatives, analgesics, anesthetics, and intoxicants, and are sometimes called somnifacients and soporifics when used to induce sleep. Hypnotics may be classed as fast-acting, intermediate-acting, or long-acting.

"Insomnia" refers to an acute or chronic sleep disorder characterized by an inability to go to sleep and/or to remain asleep for a period during the night, further characterized by an inadequate amount of sleep. Insomnia may vary in degree from restlessness or disturbed slumber to a curtailment of the normal length of sleep or to absolute wakefulness. Insomnia

may be exacerbated by secondary factors such as light, noise, or pain. Insomnia has been categorized into at least four major types, sleep onset insomnia, sleep maintenance insomnia, sleep offset insomnia, and non-restorative insomnia. See for example Czeislet *et al.* Harrison's Principles of Internal medicine, 15th Ed. Vol. 1, Braunwald, Fauci, Kasper, Hauser, Longo, Jameson, Editors; McGraw-Hill: New York, Vol 1, pp 155-163.

"Lubricants" are compounds which prevent, reduce or inhibit adhesion or friction of materials. Exemplary lubricants include, *e.g.*, stearic acid; calcium hydroxide; talc; sodium stearyl fumerate; a hydrocarbon such as mineral oil, or hydrogenated vegetable oil such as hydrogenated soybean oil (Sterotex®); higher fatty acids and their alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, glycerol, talc, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax™, sodium oleate, glyceryl behenate, polyethylene glycol, magnesium or sodium lauryl sulfate, colloidal silica such as Syloid™, Carb-O-Sil®, a starch such as corn starch, silicone oil, a surfactan, and the like.

A "measurable serum concentration" or "measurable plasma concentration" describes the blood serum or blood plasma concentration, typically measured in mg, μg, or ng of therapeutic agent per ml, dl, or l of blood serum, of a therapeutic agent that is absorbed into the bloodstream after administration. One of ordinary skill in the art would be able to measure the serum concentration or plasma concentration of a proton pump inhibitor or a sleep aid. See, *e.g.*, Gonzalez H., *et al.*, J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci., vol. 780, pp 459-65, (Nov. 25, 2002).

The term "non-benzodiazepine hypnotic" refers to a class of hypnotics whose chemical structure is dissimilar to benzodiazapine class of hypnotics. Despite a structural dissimilarity, non-benzodiazepine hypnotics also appear to be benzodiazepine receptor antagonists (BzRAs) or act on related sites. Major classes of non-benzodiazepine hypnotics include imidazopyridines and pyrazolopyrimidines. Other non-benzodiazepines are known, *e.g.*, indiplone. As with the benzodiazepine hypnotics, non-benzodiazepine hypnotics can also be classified by mode of action. Fast-acting non-benzodiazepine hypnotics include zopiclone, zolpidem or zolpidem tartarate (Ambien®), and zaleplon (Sonata®).

"Parietal cell activators" or "activators" stimulate the parietal cells and enhance the pharmaceutical activity of the proton pump inhibitor. Parietal cell activators include, *e.g.*, chocolate; alkaline substances such as sodium bicarbonate; calcium such as calcium carbonate, calcium gluconate, calcium hydroxide, calcium acetate and calcium

glycerophosphate; peppermint oil; spearmint oil; coffee; tea and colas (even if decaffeinated); caffeine; theophylline; theobromine; amino acids (particularly aromatic amino acids such as phenylalanine and tryptophan); and combinations thereof.

"Pharmacodynamics" refers to the factors which determine the biologic response observed relative to the concentration of drug at a site of action.

"Pharmacokinetics" refers to the factors which determine the attainment and maintenance of the appropriate concentration of drug at a site of action.

"Plasma concentration" refers to the concentration of a substance in blood plasma or blood serum of a subject. It is understood that the plasma concentration of a therapeutic agent may vary many-fold between subjects, due to variability with respect to metabolism of therapeutic agents. In accordance with one aspect of the present invention, the plasma concentration of a proton pump inhibitors and/or sleep aid may vary from subject to subject. Likewise, values such as maximum plasma concentraton (C_{max}) or time to reach maximum serum concentration (T_{max}), or area under the concentration curve (AUC) may vary from subject to subject. Due to this variability, the amount necessary to constitute "a therapeutically effective amount" of proton pump inhibitor, sleep aid, or other therapeutic agent, may vary from subject to subject. It is understood that when mean plasma concentrations are disclosed for a population of subjects, these mean values may include substantial variation.

"Plasticizers" are compounds used to soften the microencapsulation material or film coatings to make them less brittle. Suitable plasticizers include, *e.g.*, polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, and triacetin.

"Prevent" or "prevention" means no gastrointestinal disorder or disease development if none had occurred, or no further gastrointestinal disorder or disease development if there had already been development of the gastrointestinal disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the gastrointestinal disorder or disease.

A "prodrug" refers to a drug or compound in which the pharmacological action results from conversion by metabolic processes within the body. Prodrugs are generally drug precursors that, following administration to a subject and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by a metabolic pathway. Some prodrugs have a chemical group present on the prodrug which renders it less active and/or confers solubility or some other property to the drug. Once the

chemical group has been cleaved and/or modified from the prodrug the active drug is generated. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. The design of prodrugs to date has been to increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent. See, Fedorak, *et al.*, Am. J. Physiol, 269:G210-218 (1995); McLoed, *et al.*, Gastroenterol., 106:405-413 (1994); Hochhaus, *et al.*, Biomed. Chrom., 6:283-286 (1992); J. Larsen and H. Bundgaard, Int. J. Pharmaceutics, 37, 87 (1987); J. Larsen *et al.*, Int. J. Pharmaceutics, 47, 103 (1988); Sinkula *et al.*, J. Pharm. Sci., 64:181-210 (1975); T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

"Serum concentration" refers to the concentration of a substance such as a therapeutic agent, in blood plasma or blood serum of a subject. It is understood that the serum concentration of a therapeutic agent may vary many-fold between subjects, due to variability with respect to metabolism of therapeutic agents. In accordance with one aspect of the present invention, the serum concentration of a proton pump inhibitors and/or sleep aid may vary from subject to subject. Likewise, values such as maximum serum concentraton (C_{max}) or time to reach maximum serum concentration (T_{max}), or total area under the serum concentration curve (AUC) may vary from subject to subject. Due to this variability, the amount necessary to constitute "a therapeutically effective amount" of proton pump inhibitor, sleep aid, or other therapeutic agent, may vary from subject to subject. It is understood that when mean serum concentrations are disclosed for a population of subjects, these mean values may include substantial variation.

The term "sleep onset insomnia" refers to an inability to fall sleep. Sleep onset insomnia is characterized as requiring more than thirty minutes from bedtime to the onset of sleep.

The term "sleep maintenance insomnia" refers to an inability to remain asleep after the onset of sleep. Sleep maintenance insomnia is characterized by periodic wakeups during a sleep cycle. Wakeups may come hours apart or as frequently as every twenty seconds, depending on their cause.

The term "sleep offset insomnia" also referred to as "early-morning awakening insomnia" refers a truncated or shortened period of diurnal sleep. Early-morning awakening insomnia is characterized by a period of sleep followed by an awakening 2-3 hours prior to normal awakening time. Sufferers of this form of insomnia often cannot get back to sleep.

The term "sleeplessness" refers to any difficulty in falling asleep, remaining asleep, or achieving a full period of sleep. Sleeplessness as used herein encompasses insomnia (inadequate amount of sleep). In some cases, sleeplessness differs from insomnia in that, once a subject goes to sleep or goes back to sleep, they may achieve an adequate amount of sleep. Sleeplessness may by associated with the other disorders, *e.g.*, gastric acid disorder. For example, a subject may experience sleeplessness while experiencing the distress caused by a gastric acid related disorder, which may interfere with the ability to go to sleep or may cause awakening in a subject that is already asleep. A therapy that addresses both the gastric acid related disorder and induces sleep will provide relief from both problems. Alternately, a subject may experience sleeplessness (or insomnia) associated with the gastric acid related disorder, *e.g.*, worry about health, or anticipatory anxiety about future episodes of distress from the gastric acid related disorder. When sleeplessness is not caused by the gastric acid related disorder, but is associated with the gastric acid disorder, the subject can also benefit from a therapy that addresses both the gastric acid disorder and the sleeplessness. Sleeplessness (insomnia) may arise independently of the presence or absence of other disorders. Sleeplessness may result from worry about another disorder. In these and other cases, the subject benefits from a combination therapy that addresses both the gastric acid disorder and the sleeplessness.

"Solubilizers" include compounds such as citric acid, succinic acid, fumaric acid, malic acid, tartaric acid, maleic acid, glutaric acid, sodium bicarbonate, sodium carbonate and the like.

"Stabilizers" include compounds such as any antioxidation agents, buffers, acids, and the like.

"Suspending agents" or "thickening agents" include compounds such as polyvinylpyrrolidone, *e.g.*, polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30; polyethylene glycol, *e.g.*, the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400; sodium carboxymethylcellulose; methylcellulose; hydroxy-propylmethylcellulose; polysorbate-80; hydroxyethylcellulose; sodium alginate; gums, such as, *e.g.*, gum tragacanth and gum acacia; guar gum; xanthans, including xanthan gum; sugars; cellulosics, such as, *e.g.*, sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose; polysorbate-80; sodium alginate; polyethoxylated sorbitan monolaurate; polyethoxylated sorbitan monolaurate; povidone and the like.

"Surfactants" include compounds such as sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, *e.g.*, Pluronic® (BASF); and the like.

A "therapeutically effective amount" or "effective amount" is that amount of a pharmaceutical agent to achieve a pharmacological effect. An "effective amount" of a proton pump inhibitor is an amount effective to achieve a desired pharmacologic effect or therapeutic improvement without undue adverse side effects. For example, an effective amount of a proton pump inhibitor refers to an amount of proton pump inhibitor that reduces acid secretion, or raises gastrointestinal fluid pH, or reduces gastrointestinal bleeding, or reduces the need for blood transfusion, or improves survival rate, or provides for a more rapid recovery from a gastric acid related disorder. An "effective amount" of a sleep aid is an amount effective to achieve a desired pharmacological effect on the subject's sleep, without undue adverse side effects. For example, an effective amount of a fast-acting benzodiazepine hypnotic refers to an amount sufficient to induce sleep without undue "rebound" or residual effects. The effective amount of a pharmaceutical agent will be selected by those skilled in the art depending on the particular patient and the disease level. It is understood that "an effect amount" or "a therapeutically effective amount" can vary from subject to subject, due to variation in metabolism of therapeutic agents such as proton pump inbhibitors and/or sleep aids.

"Total intensity of aroma" is the overall immediate impression of the strength of the aroma and includes both aromatics and nose feel sensations.

"Total intensity of flavor" is the overall immediate impression of the strength of the flavor including aromatics, basic tastes and mouth feel sensations.

"Treat" or "treatment" refers to any treatment of a disorder or disease associated with a gastrointestinal disorder, such as preventing the disorder or disease from occurring in a subject which may be predisposed to the disorder or disease, but has not yet been diagnosed as having the disorder or disease; inhibiting the disorder or disease, *e.g.*, arresting the development of the disorder or disease, relieving the disorder or disease, causing regression of the disorder or disease, or relieving the condition caused by the disease or disorder, or stopping the symptoms of the disease or disorder.

"Wetting agents" include compounds such as oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan

monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, sodium lauryl sulfate, and the like.

COMBINATION THERAPY

Compositions and methods for combination therapy are provided herein. In accordance with one aspect, the pharmaceutical compositions disclosed herein are used to treat a gastric acid related disorder where treatment with a proton pump inhibitor is indicated, and to induce sleep in a subject. In one embodiment, pharmaceutical compositions disclosed herein are used treat a subject suffering from a gastric acid related disorder and sleeplessness, in particular insomnia.

Combination therapies contemplated by the present invention can be used as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of the proton pump inhibitor and the sleep aid. It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, can be modified in accordance with a variety of factors. These factors include the type of gastric acid disorder and the type of sleeplessness from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, the dosage regimen actually employed can vary widely and therefore can deviate from the dosage regimens set forth herein.

In accordance with one aspect, compositions and methods of the present invention are designed to produce release of the proton pump inhibitor to the site of delivery, while substantially preventing or inhibiting acid degradation of the proton pump inhibitor. The present invention includes compositions and methods for treating, preventing, reversing, halting or slowing the progression of a gastric acid related disorder once it becomes clinically evident, or treating the symptoms associated with or related to the gastric acid related disorder, by administering to the subject a composition of the present invention. The subject may already have a gastric acid related disorder at the time of administration, or be at risk of developing a gastric acid related disorder. The symptoms or conditions of a gastric acid related disorder in a subject can be determined by one skilled in the art and are described in standard textbooks. The method comprises the oral administration a effective amount of one or more compositions of the present invention to a subject in need thereof. Gastric acid related disorders suitable for treatment using compositions and methods of the present invention include, but are not limited to, duodenal ulcer disease, gastrointestinal ulcer disease, gastroesophageal reflux disease (GERD), erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, heartburn, esophageal disorder, and acid dyspepsia.

In accordance with another aspect, compositions and methods of the present invention are designed to deliver sleep aids to induce sleep by the mechanism of the sleep aid chosen for each embodiment. The present invention includes compositions and methods for treating sleeplessness, in particular insomnia, by administering to the subject a composition of the present invention. "Sleeplessness" includes difficulty falling asleep, insomnia (inadequate amount of sleep), and other disorders of sleep. Insomnia may be occasional or chronic. The subject may already have insomnia at the time of administration, or be at risk of developing insomnia. The symptoms or conditions of the type of insomnia suffered by the subject can be determined by one skilled in the art and are described in standard textbooks.

In accordance with one aspect, compositions and methods of the present invention are useful for treating a subject suffering from a gastric acid related disorder and associated sleeplessness. In one embodiment, compositions and methods of the present invention are used to treat a subject suffering from a gastric-acid related disorder and to induce sleep, where the distress of the gastric acid disorder is interfering with the subject's ability to go to sleep. In another embodiment, compositions and methods of the present invention are used to treat a subject suffering from a gastric-acid related disorder and to induce sleep, where the subject has been awakened by the gastric-acid reated disorder. In another embodiment, compositions and methods of the present invention are used to treat a subject suffering from a gastric-acid related disorder and to induce sleep, where worry about the gastric acid disorder is interfering with the subject's ability to go to sleep. In these and related embodiments, compositions are administered before the subject wishes to go to sleep. For a particular subject, the most appropriate formulation or method of use of a composition of the present invention may depend on the type of gastric acid disorder, the time period in which the proton pump inhibitor acts to treat the gastric acid related disorder and the time period in which the sleep aid induces sleep.

In accordance with another aspect, compositions and methods of the present invention are useful for treating a suffering from a gastric acid related disorder and insomnia, where insomnia is generally understood to refer to an inadequate amount of sleep. A subject may suffer from insomnia caused by or related to the gastric related disorder. Alternately, a subject may suffer from insomnia that is not caused by or related to the gastric acid related disorder. In one embodiment, compositions and methods of the invention are used to treat a gastric acid related disorder and induce sleep in a subject suffering from sleep onset insomnia (difficulty falling asleep). In another embodiment, compositions and methods of the invention are used to treat a gastric acid related disorder and induce sleep in a subject

suffering from sleep maintenance insomnia (frequent or sustained awakenings). In another embodiment, compositions and methods of the invention are used to treat a gastric acid related disorder and induce sleep in a subject suffering from sleep offset insomnia or morning insomnia (early morning awakening). As disclosed below, sleep aids to treat different types of insomnia are known in the art and compositions of the present invention can be formulated to induce sleep by a mechanism appropriate to treat a particular type of insomnia.

In accordance with another aspect, compositions and methods of the present invention are useful for treating a subject suffering from a gastric acid related disorder and suffering for sleeplessness, in particular insomnia, that is not associated with the gastric acid related disorder. Accordingly, compositions and methods of the present invention are useful for treating a subject who is suffering from a gastric acid related disorder and is also suffering from insomnia.

Compositions of the present invention can be formulated to treat a gastric acid related disorder and to induce sleep in accordance with one or both of the conditions for which relief is sought. As disclosed below, proton pump inhibitors can be formulated to deliver rapid relief and well as sustained relief of a gastric acid related disorder. As disclosed below, formulations of sleep aids, in particular hypnotics, can be selected to treat different kinds of insomnia on the basis of their mechanism of action.

In one embodiment, a subject is administered a composition containing a proton pump inhibitor formulated to give rapid relief for an episode of a gastric acid related disorder, and a fast-acting hypnotic to induce sleep quickly. According to methods of the present invention, this composition may be administered before starting to sleep, or may be administered after a subject has been awakened by an episode of a gastric acid related disorder. Further, when the subject has awakened, the choice of sleep aid may be influenced by the amount of time the subject has for sleeping after going back to sleep.

In another embodiment, a subject is administered a composition including uncoated proton pump inhibitor formulated to provide rapid relief and coated proton pump inhibitor to prevent or treat recurring episodes of the gastric acid related disorder during sleep, where the composition also contains an intermediate-acting hypnotic to induce sleep maintenance. According to the methods of the present invention, this composition is administered before starting to sleep, and the subject remains asleep.

In another embodiment, a composition containing a long-acting hypnotic is administered to a subject suffers from a gastric acid related disorder and also suffers from sleep offset insomnia (early morning awakening). According to the methods of the invention,

the formulation of the proton pump inhibitor is chosen on the basis of the type of gastric acid related disorder suffered by the subject.

The pharmaceutical agents which make up the combination therapy disclosed herein may be a combined dosage form or in separate dosage forms intended for substantially simultaneous administration. The pharmaceutical agents that make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two step administration. Thus, a regimen may call for sequential administration, spaced-apart administration of the separate, active agents. The time period between the multiple administration steps may range from, a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent. Circadian variation of the target molecule concentration may also determine the optimal dose interval.

PROTON PUMP INHIBITORS

The terms "proton pump inhibitor," "PPI," and "proton pump inhibiting agent" can be used interchangeably to describe any acid labile pharmaceutical agent possessing pharmacological activity as an inhibitor of H+/K+-ATPase. A proton pump inhibitor may, if desired, be in the form of free base, free acid, salt, ester, hydrate, anhydrate, amide, enantiomer, isomer, tautomer, prodrug, polymorph, derivative, or the like, provided that the free base, salt, ester, hydrate, amide, enantiomer, isomer, tautomer, prodrug, or any other pharmacologically suitable derivative is therapeutically active.

In various embodiments, the proton pump inhibitor can be a substituted bicyclic aryl-imidazole, wherein the aryl group can be, *e.g.*, a pyridine, a phenyl, or a pyrimidine group and is attached to the 4- and 5-positions of the imidazole ring. Proton pump inhibitors comprising a substituted bicyclic aryl-imidazoles include, but are not limited to, omeprazole, hydroxyomeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, and tenatoprazole, ransoprazole, pariprazole, leminoprazole, or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative thereof. (See, *e.g.*, *The Merck Index*, Merck & Co. Rahway, N.J. (2001)).

Other proton pump inhibitors include but are not limited to: soraprazan (Altana); ilaprazole (U.S. Patent No. 5,703,097) (Il-Yang); AZD-0865 (AstraZeneca); YH-1885 (PCT Publication WO 96/05177) (SB-641257) (2-pyrimidinamine, 4-(3,4-dihydro-1-methyl-2(1H)-isoquinolinyl)-N-(4-fluorophenyl)-5,6-dimethyl-, monohydrochloride) (YuHan); BY-112

(Altana); SPI-447 (Imidazo(1,2-a)thieno(3,2-c)pyridin-3-amine,5-methyl-2-(2-methyl-3-thienyl) (Shinnippon); 3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano(2,3-c)-imidazo(1,2-a)pyridine (PCT Publication WO 95/27714) (AstraZeneca); Pharmaprojects No. 4950 (3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro-pyrano(2,3-c)-imidazo(1,2-a)pyridine) (AstraZeneca, ceased) WO 95/27714; Pharmaprojects No. 4891 (EP 700899) (Aventis); Pharmaprojects No. 4697 (PCT Publication WO 95/32959) (AstraZeneca); H-335/25 (AstraZeneca); T-330 (Saitama 335) (Pharmacological Research Lab); Pharmaprojects No. 3177 (Roche); BY-574 (Altana); Pharmaprojects No. 2870 (Pfizer); AU-1421 (EP 264883) (Merck); AU-2064 (Merck); AY-28200 (Wyeth); Pharmaprojects No. 2126 (Aventis); WY-26769 (Wyeth); pumaprazole (PCT Publication WO 96/05199) (Altana); YH-1238 (YuHan); Pharmaprojects No. 5648 (PCT Publication WO 97/32854) (Dainippon); BY-686 (Altana); YM-020 (Yamanouchi); GYKI-34655 (Ivax); FPL-65372 (Aventis); Pharmaprojects No. 3264 (EP 509974) (AstraZeneca); nepaprazole (Toa Eiyo); HN-11203 (Nycomed Pharma); OPC-22575; pumilacidin A (BMS); saviprazole (EP 234485) (Aventis); SKandF-95601 (GSK, discontinued); Pharmaprojects No. 2522 (EP 204215) (Pfizer); S-3337 (Aventis); RS-13232A (Roche); AU-1363 (Merck); SKandF-96067 (EP 259174) (Altana); SUN 8176 (Daiichi Phama); Ro-18-5362 (Roche); ufiprazole (EP 74341) (AstraZeneca); and Bay-p-1455 (Bayer); or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative of these compounds.

Still other proton pump inhibitors contemplated by the present invention include those described in the following U.S. Patent Nos: 4,628,098; 4,689,333; 4,786,505; 4,853,230; 4,965,269; 5,021,433; 5,026,560; 5,045,321; 5,093,132; 5,430,042; 5,433,959; 5,576,025; 5,639,478; 5,703,110; 5,705,517; 5,708,017; 5,731,006; 5,824,339; 5,855,914; 5,879,708; 5,948,773; 6,017,560; 6,123,962; 6,187,340; 6,296,875; 6,319,904; 6,328,994; 4,255,431; 4,508,905; 4,636,499; 4,738,974; 5,690,960; 5,714,504; 5,753,265; 5,817,338; 6,093,734; 6,013,281; 6,136,344; 6,183,776; 6,328,994; 6,479,075; 6,559,167.

Other substituted bicyclic aryl-imidazole compounds as well as their salts, hydrates, esters, amides, enantiomers, isomers, tautomers, polymorphs, prodrugs, and derivatives may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry. See, *e.g.*, *March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th Ed. (New York: Wiley-Interscience, 1992); Leonard *et al.*, *Advanced Practical Organic Chemistry*, (1992); Howarth et al; *Core Organic Chemistry* (1998); and Weisermel *et al.*, *Industrial Organic Chemistry* (2002).

"Pharmaceutically acceptable salts," or "salts," include, *e.g.*, the salt of a proton pump inhibitor prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic, methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

In one embodiment, acid addition salts are prepared from the free base using conventional methodology involving reaction of the free base with a suitable acid. Suitable acids for preparing acid addition salts include both organic acids, *e.g.*, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

In other embodiments, an acid addition salt is reconverted to the free base by treatment with a suitable base. In a further embodiment, the acid addition salts of the proton pump inhibitors are halide salts, which are prepared using hydrochloric or hydrobromic acids. In still other embodiments, the basic salts are alkali metal salts, *e.g.*, sodium salt and copper salt.

Salt forms of proton pump inhibiting agents include, but are not limite to: a sodium salt form such as esomeprazole sodium, omeprazole sodium, rabeprazole sodium, pantoprazole sodium; or a magnesium salt form such as esomeprazole magnesium or omeprazole magnesium, described in U.S. Patent No. 5,900,424; a calcium salt form; or a potassium salt form such as the potassium salt of esomeprazole, described in U.S. Patent Appln. No. 02/0198239 and U.S. Patent No. 6,511,996. Other salts of esomeprazole are described in U.S. 4,738,974 and U.S. 6,369,085. Salt forms of pantoprazole and lansoprazole are discussed in U.S. Pat. Nos. 4,758,579 and 4,628,098, respectively.

In one embodiment, preparation of esters involves functionalization of hydroxyl and/or carboxyl groups which may be present within the molecular structure of the drug. In one embodiment, the esters are acyl-substituted derivatives of free alcohol groups, *e.g.*, moieties derived from carboxylic acids of the formula $RCOOR_1$ where R_1 is a lower alkyl group. Esters can be reconverted to the free acids, if desired, by using conventional procedures such as hydrogenolysis or hydrolysis.

"Amides" may be prepared using techniques known to those skilled in the art or described in the pertinent literature. For example, amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with an amine group such as ammonia or a lower alkyl amine.

"Tautomers" of substituted bicyclic aryl-imidazoles include, *e.g.*, tautomers of omeprazole such as those described in U.S. Patent Nos.: 6,262,085; 6,262,086; 6,268,385; 6,312,723; 6,316,020; 6,326,384; 6,369,087; and 6,444,689; and U.S. Patent Publication No. 02/0156103.

An exemplary "isomer" of a substituted bicyclic aryl-imidazole is the isomer of omeprazole including but not limited to isomers described in: Oishi *et al.*, Acta Cryst. (1989), C45, 1921-1923; U.S. Patent No. 6,150,380; U.S. Patent Publication No. 02/0156284; and PCT Publication No. WO 02/085889.

Exemplary "polymorphs" include, but are not limited to those described in PCT Publication No. WO 92/08716, and U.S. Patent Nos. 4,045,563; 4,182,766; 4,508,905; 4,628,098; 4,636,499; 4,689,333; 4,758,579; 4,783,974; 4,786,505; 4,808,596; 4,853,230; 5,026,560; 5,013,743; 5,035,899; 5,045,321; 5,045,552; 5,093,132; 5,093,342; 5,433,959; 5,464,632; 5,536,735; 5,576,025; 5,599,794; 5,629,305; 5,639,478; 5,690,960; 5,703,110; 5,705,517; 5,714,504; 5,731,006; 5,879,708; 5,900,424; 5,948,773; 5,997,903; 6,017,560; 6,123,962; 6,147,103; 6,150,380; 6,166,213; 6,191,148; 5,187,340; 6,268,385; 6,262,086; 6,262,085; 6,296,875; 6,316,020; 6,328,994; 6,326,384; 6,369,085; 6,369,087; 6,380,234; 6,428,810; 6,444,689; and 6,462,0577.

Micronized Proton Pump Inhibitor

Particle size of the proton pump inhibitor can affect the solid dosage form in numerous ways. Since decreased particle size increases in surface area (S), the particle size reduction provides an increase in the rate of dissolution (dM/dt) as expressed in the Noyes-Whitney equation below:

$$dM/dt = dS / h(Cs-C)$$

M =mass of drug dissolved; t = time; D = diffusion coefficient of drug; S = effective surface area of drug particles; H= stationary layer thickness; Cs = concentration of solution at saturation; and C = concentration of solution at time t.

Because omeprazole, as well as other proton pump inhibitors, has poor water solubility, to aid the rapid absorption of the drug product, various embodiments of the present invention use micronized proton pump inhibitor is used in the drug product formulation.

In some embodiments, the average particle size of at least about 90% the micronized proton pump inhibitor is less than about 40 μm, or less than about 35 μm, or less than about 30 μm, or less than about 25 μm, or less than about 20 μm, or less than about 15 μm, or less than about 10 μm. In other embodiments, at least 80% of the micronized proton pump inhibitor has an average particle size of less than about 40 μm, or less than about 35 μm, or less than about 30 μm, or less than about 25 μm, or less than about 20 μm, or less than about 15 μm, or less than about 10 μm. In still other embodiments, at least 70% of the micronized proton pump inhibitor has an average particle size of less than about 40 μm, or less than about 35 μm, or less than about 30 μm, or less than about 25 μm, or less than about 20 μm, or less than about 15 μm, or less than about 10 μm.

Compositions are provided wherein the micronized proton pump inhibitor is of a size which allows greater than 75% of the proton pump inhibitor to be released within about 1 hour, or within about 50 minutes, or within about 40 minutes, or within about 30 minutes, or within about 20 minutes, or within about 10 minutes or within about 5 minutes of dissoluion testing. In another embodiment of the invention, the micronized proton pump inhibitor is of a size which allows greater than 90% of the proton pump inhibitor to be released within about 1 hour, or within about 50 minutes, or within about 40 minutes, or within about 30 minutes, or within about 20 minutes, or within about 10 minutes or within about 5 minutes of dissoluion testing. *See* U.S. Provisional Application No. 60/488,324 filed July 18, 2003, and any subsequent application claiming priority to this application, all of which are incorporated by reference in their entirety.

BUFFERING AGENTS

The pharmaceutical composition of the invention comprises one or more buffering agents. A class of buffering agents useful in the present invention include, but are not limited to, buffering agents possessing pharmacological activity as a weak base or a strong base. In one embodiment, the buffering agent, when formulated or delivered with an proton pump inhibiting agent, functions to substantially prevent or inhibit the acid degradation of the proton pump inhibitor by gastrointestinal fluid for a period of time, *e.g.*, for a period of time sufficient to preserve the bioavailability of the proton pump inhibitor administered. The buffering agent can be delivered before, during and/or after delivery of the proton pump inhibitor. In one aspect of the present invention, the buffering agent includes a salt of a Group IA metal, including, *e.g.*, a bicarbonate salt of a Group IA metal, a carbonate salt of a Group IA metal, an alkali earth metal buffering agent, an aluminum buffering agent, a calcium buffering agent, or a magnesium buffering agent.

Other buffering agents suitable for the present invention include, *e.g.*, alkali (sodium and potassium) or alkali earth (calcium and magnesium) carbonates, phosphates, bicarbonates, citrates, borates, acetates, phthalates, tartrate, succinates and the like, such as sodium or potassium phosphate, citrate, borate, acetate, bicarbonate and carbonate.

In various embodiments, a buffering agent includes an amino acid, an acid salt of an amino acid, an alkali salt of an amino acid, aluminum hydroxide, aluminum hydroxide/magnesium carbonate/calcium carbonate co-precipitate, aluminum magnesium hydroxide, aluminum hydroxide/magnesium hydroxide co-precipitate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, calcium acetate, calcium bicarbonate, calcium borate, calcium carbonate, calcium citrate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium lactate, calcium phthalate, calcium phosphate, calcium succinate, calcium tartrate, dibasic sodium phosphate, dipotassium hydrogen phosphate, dipotassium phosphate, disodium hydrogen phosphate, disodium succinate, dry aluminum hydroxide gel, L-arginine, magnesium acetate, magnesium aluminate, magnesium borate, magnesium bicarbonate, magnesium carbonate, magnesium citrate, magnesium gluconate, magnesium hydroxide, magnesium lactate, magnesium metasilicate aluminate, magnesium oxide, magnesium phthalate, magnesium phosphate, magnesium silicate, magnesium succinate, magnesium tartrate, potassium acetate, potassium carbonate, potassium bicarbonate, potassium borate, potassium citrate, potassium metaphosphate, potassium phthalate, potassium phosphate, potassium polyphosphate, potassium pyrophosphate, potassium succinate, potassium tartrate, sodium acetate, sodium bicarbonate, sodium borate, sodium carbonate, sodium citrate, sodium gluconate, sodium hydrogen phosphate, sodium hydroxide, sodium lactate, sodium phthalate, sodium phosphate, sodium polyphosphate, sodium pyrophosphate, sodium sesquicarbonate, sodium succinate, sodium tartrate, sodium tripolyphosphate, synthetic hydrotalcite, tetrapotassium pyrophosphate, tetrasodium pyrophosphate, tripotassium phosphate, trisodium phosphate, and trometamol. (See, *e.g.*, lists provided in *The Merck Index*, Merck & Co. Rahway, N.J. (2001)). Certain proteins or protein hydrolysates that rapidly neutralize acids can serve as buffering agents in the present invention. Combinations of the above mentioned buffering agents can be used in the pharmaceutical compositions described herein.

The buffering agents useful in the present invention also include buffering agents or combinations of buffering agents that interact with HCl (or other acids in the environment of interest) faster than the proton pump inhibitor interacts with the same acids. When placed in a

liquid phase, such as water, these buffering agents produce and maintain a pH greater than the pKa of the proton pump inhibitor.

In various embodiments, the buffering agent is selected from sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium oxide, magnesium hydroxide, magnesium carbonate, aluminum hydroxide, and mixtures thereof. In another embodiment, the buffering agent is sodium bicarbonate and is present in about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg proton pump inhibitor. In yet another embodiment, the buffering agent is a mixture of sodium bicarbonate and magnesium hydroxide, wherein the sodium bicarbonate and magnesium hydroxide are each present in about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg proton pump inhibitor. In still another embodiment, the buffering agent is a mixture of sodium bicarbonate, calcium carbonate, and magnesium hydroxide, wherein the sodium bicarbonate, calcium carbonate, and magnesium hydroxide are each present in about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg of the proton pump inhibitor.

In various other embodiments of the present invention, the buffering agent is present in an amount of about 0.1 mEq/mg to about 5 mEq/mg of the proton pump inhibitor, or about 0.5 mEq/mg to about 3 mEq/mg of the proton pump inhibitor, or about 0.6 mEq/mg to about 2.5 mEq/mg of the proton pump inhibitor, or about 0.7 mEq/mg to about 2.0 mEq/mg of the proton pump inhibitor, or about 0.8 mEq/mg to about 1.8 mEq/mg of the proton pump inhibitor, or about 1.0 mEq/mg to about 1.5 mEq/mg of the proton pump inhibitor, or at least 0.5 mEq/mg of the proton pump inhibitor.

In one embodiment, the buffering agent is present in the pharmaceutical compositions of the present invention in an amount of about 1 mEq to about 160 mEq per dose, or about 5 mEq, or about 10 mEq, or about 15 mEq, or about 20 mEq, or about 25 mEq, or about 30 mEq, or about 35 mEq, or about 40 mEq, or about 45 mEq, or about 50 mEq, or about 60 mEq, or about 70 mEq, or about 80 mEq, or about 90 mEq, or about 100 mEq, or about 110 mEq, or about 120 mEq, or about 130 mEq, or about 140 mEq, or about 150 mEq, or about 160 mEq per dose.

In one embodiment, the pharmaceutical composition comprises between about 5 mEq to about 20 mEq, or between about 5 mEq to about 15 mEq, or between about 5 mEq to about 12 mEq, or between about 7 mEq to about 12 mEq of buffering agent, wherein the pharmaceutical composition is substantially free from amino acids. In another embodiment, the pharmaceutical composition comprises about 5 mEq, or about 7 mEq, or about 10 mEq, or about 12 mEq, or about 15 mEq, or about 17 mEq, or about 20 mEq of buffering agent, wherein the pharmaceutical composition is substantially free from amino acids.

In another embodiment, the buffering agent is present in the composition in an amount, on a weight to weight (w/w) basis, of more than about 5 times, or more than about 10 times, or more than about 20 times, or more than about 30 times, or more than about 40 times, or more than about 50 times, or more than about 60 times, or more than about 70 times, or more than about 80 times, or more than about 90 times, or more than about 100 times the amount of the proton pump inhibiting agent.

In another embodiment, the amount of buffering agent present in the pharmaceutical composition is between 200 and 3500 mg. In other embodiments, the amount of buffering agent present in the pharmaceutical composition is about 200 mgs, or about 300 mgs, or about 400 mgs, or about 500 mgs, or about 600 mgs, or about 700 mgs, or about 800 mgs, or about 900 mgs, or about 1000 mgs, or about 1100 mgs, or about 1200 mgs, or about 1300 mgs, or about 1400 mgs, or about 1500 mgs, or about 1600 mgs, or about 1700 mgs, or about 1800 mgs, or about 1900 mgs, or about 2000 mgs, or about 2100 mgs, or about 2200 mgs, or about 2300 mgs, or about 2400 mgs, or about 2500 mgs, or about 2600 mgs, or about 2700 mgs, or about 2800 mgs, or about 2900 mgs, or about 3000 mgs, or about 3200 mgs, or about 3500 mgs.

SLEEP AIDS

Sleep aids may be categorized as hypnotics (sleep-inducing compounds) and sleep aids that otherwise aid or facilitate sleep. Hypnotics include, but are not limited to, benzodiazepine hypnotics, non-benzodiazepine hypnotic, antihistamine hypnotics, barbiturates, peptide hypnotics, and herbal extracts. Hypnotics are further classified as fast-acting, intermediate-acting, and long-acting. Fast-acting hypnotics (also called short-acting hypnotics) allow a subject to go to sleep or return to sleep (to complete a sleep period), and are therefore useful for treating sleep disorders associated with difficulty falling asleep or returning to sleep such as sleep onset insomnia. In particular, fast-acing hypotics are useful for treating sleep disorders associated with one or more episode(s) of gastric acid related disorder that prevent or interrupt sleep. Intermediate-acting hypnotics induce sleep maintenance, and are therefore useful for treating an inability to stay asleep. In particular, intermediate-acting hypnotics are useful for treating sleeplessness associated with a gastric acid related disorder that interferes with ability to stay asleep. Long-acting hypnotics induce sleep by preventing early morning awakening that interrupts the completion of a full sleep period, *e.g.*, as seen in sleep offset insomnia. In particular, long-acting hypnotics are useful for treating sleeplessness associated with gastric acid related disorders, wherein the gastric acid related disorder causes early morning awakening.

Herbal extracts of valerian, chamomile, lavender oil, hops, and/or passion-flower, may act as sleep-inducing hypnotics, or may facilitate sleep by inducing relaxation. Peptide hypnotics include gabapeptin, as described in U.S. Patent No. 6,372,792. Peptide hormones useful as sleep aids incude melatonin. The amino acid tryptophan is known to have a sedative effect.

Sleep aids can be formulated to achieve desired therapeutic effects. In particular, sleep aids can be formulated for a defined release profile such as controlled release or pulsed release, *e.g.*, as described in U.S. Patent No. 6,485,792. Controlled release formations may include at least one release retardant that controls the rate of release of the hypnotic following administration to a patient. Pulsed release formulations may be used to deliver multiple doses of a hypnotic at specified times, *e.g.* to promote both rapid sleep onset and sleep maintenance using a single dose administered before retiring. Goals for a formulation may further include preventing unwanted side effects. In one embodiment, a pulsed release formulation of short-acting hypnotic not only rapidly induces sleep but also maintains sleep and avoids the next-day residual effects (also called "hangover" effects) often seen with the longer-acting hypnotics commonly used for sleep maintenance. In one embodiment, a fast-acting hypnotic useful for promoting rapid sleep onset has been formulated to produce a "pulsed" plasma profile such that a first maximum plasma concentration of the hypnotic occurs from 0.1 to 2 hours following administration, a minimum plasma concentration occurs from 2 to 4 hours following administration, a second maximum plasma concentration occurs between 4 to 6 hours following administration, and the concentration of hypnotic at 6 to 8 hours after administration is very low.

Commonly Used Sleep Aids:

The following table represents a partial listing of sleep aids suitable for the present invention. One of skill in the art will understand that any sleep aid that has been approved for usein human could be used in the compositions and methods of the present invention.

TABLE 1

REPRESENTATIVE SLEEP AIDS AND THEIR EFFECTIVE DOSAGES*

Generic name	Brand Name	Mode of Action (Onset)	Effective Dose
Benzodiazepines			
Alprazolam	Xanax	Fast to intermediate-acting	Tablet: 0.25-2 mg; Oral solution: 1mg/mL
Chlordiazepoxide	Librium	Intermediate-	Tablet: 5-10 mg;

Generic name	Brand Name	Mode of Action (Onset)	Effective Dose
		acting	Capsule 5-25 mg
Clonazepam	Klonopin, Rivotril	Long-acting	Tablet: 0.5-2 mg;
Clorazepate	Tranxene	Fast-acting	Tablet: 3.75-15 mg
Ciazepam	Valium Valrelease T-Quil	Fast-acting	Tablet: 2-10 mg Oral Solution: 1-5 mg/mL
Estazolam	ProSom	Fast-acting	Tablet: 1-2 mg
Flurazepam	Dalmane	Fast-acting	Capsule: 15-30 mg
Flunitrazepam	Rohypnol	Fast-acting	Tablet 1-2 mg
Halazepam	Paxipam	Intermediate-acting	Oral dose: 20-40 mg
Loprazolam	Dormonoct Havlane Sonin	Fast-acting	Tablet: 1 mg
Lorazepam	Ativan	Intermediate-acting	Tablet: 0.5-2 mg
Lormetazepam	Ergocalm Lembrol Loramet Loretam Notamid	Fast-acting	Tablet: 1-2 mg
Midazolam	Midazolam Dormicum	Fast-acting	Tablet: 7.5 mg
Nitrazepam	Mogadan Eatan N		Tablet: 5-10 mg
Oxazepam	Serax	Intermediate to long-acting	Capsule: 10-30 mg
Prazepam	Centrax	Long-acting	Tablet: 10 mg Capsule: 2-5 mg
Quazepam	Doral	Fast-acting	
Temazepam	Restoril	Intermediate to long-acting	Capsule: 7.5-30 mg
Triazolam	Halcion	Fast-acting	Tablet: 0.125-0.25 mg
Non-benzodiazepines			
Eszoplicone	Estorra		Tablet: 5mg
Indiplon/indiplone			Capsule: 10-30 mg
Zaleplon L-846, CL-284846, CL-284859, L-846, LJC-10846, Quilor	Sonata	Fast-acting	Capsule: 5-20 mg
Zopiclone	Imovane	Fast-acting	Tablet: 7.5 mg
Zolpidem tartrate	Ambien	Fast-acting	Tablet: 5-10 mg
Antihistamines			
Diphenhydramine	Benadryl	Intermediate- to long-acting	Tablet: 10-25 mg
Hydroxyzine	Atarax		Tablet: 10-100 mg

Generic name	Brand Name	Mode of Action (Onset)	Effective Dose
Barbiturates			
Secobarbital	Seconal	Fast-acting	Capsule: 8-250 mg
Pentobarbital	Nembutal Pentobarbitone	Fast-acting	Oral or rectal: 15-200 mg

*For other dosages see any recent Physician's Desk Reference

STABILITY ENHANCERS

Stability enhancers are described in U.S. Application No. 10/893,203 filed July 16, 2004, which is incorporated herein by reference in its entirety.

In accordance with one aspect of the present invention, compositions may include microencapsulation of one or more of: the proton pump inhibitor; the sleep aid; or the buffering agent, in order to enhance the shelf-life of the composition. Materials useful for enhancing the shelf-life of the pharmaceutical compositions of the present invention include materials compatible with the proton pump inhibitor of the pharmaceutical compositions which sufficiently isolate the proton pump inhibitor from other non-compatible excipients. Materials compatible with the proton pump inhibitors of the present invention are those that enhance the shelf-life of the proton pump inhibitor, *i.e.*, by slowing or stopping degradation of the proton pump inhibitor.

Exemplary microencapsulation materials useful for enhancing the shelf-life of pharmaceutical compositions comprising a proton pump inhibitor include, but are not limited to: cellulose hydroxypropyl ethers (HPC) such as Klucel®, Nisswo HPC and PrimaFlo HP22; low-substituted hydroxypropyl ethers (L-HPC); cellulose hydroxypropyl methyl ethers (HPMC) such as Seppifilm-LC, Pharmacoat®, Metolose SR, Opadry YS, PrimaFlo, MP3295A, Benecel MP824, and Benecel MP843; methylcellulose polymers such as Methocel® and Metolose®; Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease®; Polyvinyl alcohol (PVA) such as Opadry AMB; hydroxyethylcelluloses such as Natrosol®; carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualon®-CMC; polyvinyl alcohol and polyethylene glycol co-polymers such as Kollicoat IR®; monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit® EPO, Eudragit® RD100, and Eudragit® E100; cellulose acetate phthalate; sepifilms such as mixtures of HPMC and stearic acid, cyclodextrins; and mixtures of these materials.

In various embodiments, a buffering agent such as sodium bicarbonate is incorporated into the microencapsulation material. In other embodiments, an antioxidant such as BHT is incorporated into the microencapsulation material. In still other embodiments, plasticizers such as polyethylene glycols, *e.g.*, PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, and triacetin are incorporated into the microencapsulation material. In other embodiments, the microencapsulating material useful for enhancing the shelf-life of the pharmaceutical compositions is from the USP or the National Formulary (NF).

In further embodiments, one or more other compatible materials are present in the microencapsulation material. Exemplary materials include, but are not limited to, pH modifiers, parietal cell activators, erosion facilitators, diffusion facilitators, anti-adherents, anti-foaming agents, antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filing agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

According to one aspect of the invention, the proton pump inhibitor, buffering agent and/or sleep aid is coated. The coating may be, for example, a gastric resistant coating such as an enteric coating (*See, e.g,* WO91/16895 and WO91/16886), a controlled-release coating, an enzymatic-controlled coating, a film coating, a sustained-release coating, an immediate-release coating, or a delayed-release coating. According to another aspect of the invention, the coating may be useful for enhancing the stability of the pharmaceutical compositons of the present invention.

A pharmaceutical composition of the present invention may have an enhanced shelf-life stability if, *e.g.*, the microencapsulated proton pump inhibitor has less than about 0.5% degradation after one month of storage at room temperature, or less than about 1% degradation after one month at room temperature, or less than about 1.5% degradation after one month of storage at room temperature, or less than about 2% degradation after one month storage at room temperature, or less than about 2.5% degradation after one month of storage at room temperature, or less than about 3% degradation after one month of storage at room temperature.

In other embodiments, a pharmaceutical composition of the present invention may have an enhanced shelf-life stability if the pharmaceutical composition contains less than about 5% total impurities after about 3 years of storage, or after about 2.5 years of storage, or about 2 years of storage, or about 1.5 years of storage, or about 1 year of storage, or after 11 months of storage, or after 10 months of storage , or after 9 months of storage, or after 8

months of storage, or after 7 months of storage, or after 6 months of storage, or after 5 months of storage, or after 4 months of storage, or after 3 months of storage, or after 2 months of storage, or after 1 month of storage.

In further embodiments, a pharmaceutical compositions of the present invention may have an enhanced shelf-life stability if the pharmaceutical composition contains less degradation of the proton pump inhibitor than proton pump inhibitor in the same formulation which is not microencapsulated, sometimes referred to as "bare." For example, if bare proton pump inhibitor in the pharmaceutical composition degrades at room temperature by more than about 2% after one month of storage and the microencapsulated material degrades at room temperature by less than about 2% after one month of storage, then the proton pump inhibitor has been microencapsulated with a compatible material that enhances the shelf-life of the pharmaceutical composition.

In some embodiments, the microencapsulating material useful for enhancing the shelf-life of the pharmaceutical compositions increases the shelf-life stability of the pharmaceutical composition for at least about 5 days at room temperature, or at least about 10 days at room temperature, or at least about 15 days at room temperature, or at least about 20 days at room temperature, or at least about 25 days at room temperature, or at least about 30 days at room temperature or at least about 2 months at room temperature, or at least about 3 months at room temperature, or at least about 4 months at room temperature, or at least about 5 months at room temperature, or at least about 6 months at room temperature, or at least about 7 months at room temperature, or at least about 8 months at room temperature or at least about 9 months at room temperature, or at least about 10 months at room temperature, or at least about 11 months at room temperature, or at least about one year at room temperature, or at least about 1.5 years at room temperature, or at least about 2 years at room temperature, or at least about 2.5 years at room temperature, or about 3 years at room temperature.

In some embodiments of the present invention, the final formulation of the pharmaceutical composition will be in the form of a tablet and at least about 50%, or at least about 55%, or at least about 60%, or at least about 65%, or at least about 70%, or at least about 75%, or at least about 80%, or at least about 85% or at least about 90%, or at least about 92%, or at least about 95%, or at least about 98%, or at least about 99% of the microspheres survive the tableting process, wherein microspheres that have survived the manufacturing process are those which provide the desired properties described herein.

In other embodiments, the final formulation of the pharmaceutical composition is in the form of a powder for oral suspension and the microencapsulation material surrounding

the proton pump inhibitor will sufficiently dissolve in water, with or without stirring, in less than 1 hour, or less than 50 minutes, or less than 40 minutes, or less than 30 minutes, or less than 25 minutes, or less than 20 minutes, or less than 15 minutes, or less than 10 minutes or less than 5 minutes, or less than 1 minute. Sufficiently dissolves means that at least about 50% of the encapsulation material has dissolved.

In various embodiments the microencapsulating material useful for enhancing the shelf-life of the pharmaceutical composition sufficiently disintegrates to release the proton pump inhibitor into the gastrointestinal fluid of the stomach within less than about 1.5 hours, or within about 10 minutes, or within about 20 minutes, or within about 30 minutes, or within about or within about 40 minutes, or within about 50 minutes, or within about 1 hour, or within about 1.25 hours, or within about 1.5 hours after exposure to the gastrointestinal fluid. Sufficiently disintegrates means that at least about 50% of the microencapsulation material has dissolved.

TASTE-MASKING MATERIALS

Taste-masking materials are described in U.S. Application No. 10/893,203 filed July 16, 2004 which is incorporated by reference herein in its entirety.

In accordance with another aspect, compositions and methods of the present invention may include taste-masking materials to enhance the taste of the composition. Proton pump inhibitors are inherently bitter tasting and in one embodiment of the present invention, these bitter proton pump inhibitors are microencapsulated with a taste-masking material. Materials useful for masking the taste of pharmaceutical compositions include those materials capable of microencapsulating the proton pump inhibitor, thereby protecting the senses from its bitter taste. Taste-masking materials of the present invention provide superior pharmaceutical compositions by *e.g.*, creating a more palatable pharmaceutical composition as compared to pharmaceutical compositions and/or by creating a dosage form requiring less of the traditional flavoring agents.

The "flavor leadership" criteria used to develop a palatable product include (1) immediate impact of identifying flavor, (2) rapid development of balanced, full flavor, (3) compatible mouth feel factors, (4) no "off" flavors, and (5) short aftertaste. See, *e.g.*, Worthington, *A Matter of Taste, Pharmaceutical Executive* (April 2001). The pharmaceutical compositions of the present invention improve upon one or more of these criteria.

There are a number of known methods to determine the effect of a taste-masking material such as discrimination tests for testing differences between samples and for ranking a series of samples in order of a specific characteristic; scaling tests used for scoring the

specific product attributes such as flavor and appearance; expert tasters used to both quantitatively and qualitatively evaluate a specific sample; affective tests for either measuring the response between two products, measuring the degree of like or dislike of a product or specific attribute, or determine the appropriateness of a specific attribute; and descriptive methods used in flavor profiling to provide objective description of a product are all methods used in the field.

Different sensory qualities of a pharmaceutical composition such as aroma, flavor, character notes, and aftertaste can be measured using tests know in the art. See, *e.g.*, Roy *et al.*, *Modifying Bitterness: Mechanism, Ingredients, and Applications* (1997). For example, aftertaste of a product can be measured by using a time vs. intensity sensory measurement. And recently, modern assays have been developed to alert a processor of formulations to the bitter taste of certain substances. Using information known to one of ordinary skill in the art, one would readily be able to determine whether one or more sensory quality of a pharmaceutical composition of the present invention has been improved by the use of the taste-masking material.

Taste of a pharmaceutical composition is important for both increasing patient compliance as well as for competing with other marketed products used for similar diseases, conditions and disorders. Taste, especially bitterness, is particularly important in pharmaceutical compositions for children since, because they cannot weigh the positive, getting better, against the immediate negative, the bitter taste in their mouth, they are more likely to refuse a drug that tastes bad. Thus, for pharmaceutical compositions for children, it becomes even more important to mask the bitter taste. Microencapsulation of the proton pump inhibitor can (1) lower the amount of flavoring agents necessary to create a palatable product and/or (2) mask the bitter taste of the proton pump inhibitor by separating the drug from the taste receptors.

Taste-masking materials include, but are not limited to: cellulose hydroxypropyl ethers (HPC) such as Klucel®, Nisswo HPC and PrimaFlo HP22; low-substituted hydroxypropyl ethers (L-HPC); cellulose hydroxypropyl methyl ethers (HPMC) such as Seppifilm-LC, Pharmacoat®, Metolose SR, Opadry YS, PrimaFlo, MP3295A, Benecel MP824, and Benecel MP843; methylcellulose polymers such as Methocel® and Metolose®; Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease®; Polyvinyl alcohol (PVA) such as Opadry AMB; hydroxyethylcelluloses such as Natrosol®; carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualon®-CMC; polyvinyl alcohol and polyethylene glycol co-polymers such as Kollicoat IR®;

monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit® EPO, Eudragit® RD100, and Eudragit® E100; cellulose acetate phthalate; sepifilms such as mixtures of HPMC and stearic acid, cyclodextrins, and mixtures of these materials.

In other embodiments of the present invention, additional taste-masking materials contemplated are those described in U.S. Pat. Nos. 4,851,226, 5,075,114, and 5,876,759. For further examples of taste-masking materials, see, *e.g.*, *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed. (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, Pennsylvania 1975); Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (Marcel Decker, New York, N.Y., 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins1999).

In various embodiments, a buffering agent such as sodium bicarbonate is incorporated into the microencapsulation material. In other embodiments, an antioxidant such as BHT is incorporated into the microencapsulation material. In yet another embodiment, sodium chloride is incorporated into the taste masking material. In still other embodiments, plasticizers such as polyethylene glycol and/or stearic acid are incorporated into the microencapsulation material.

In further embodiments, one or more other compatible materials are present in the microencapsulation material. Exemplary materials include, *e.g.*, pH modifiers, parietal cell activators, erosion facilitators, diffusion facilitators, anti-adherents, anti-foaming agents, antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filing agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents.

In addition to microencapsulating the proton pump inhibitors with a taste-masking material as described herein, the pharmaceutical compositions of the present invention may also comprise one or more flavoring agents.

"Flavoring agents" or "sweeteners" useful in the pharmaceutical compositions of the present invention include, *e.g.*, acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium

glyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sucralose, sorbitol, swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, *e.g.*, anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof. In other embodiments, sodium chloride is incorporated into the pharmaceutical composition. Based on the proton pump inhibitor, buffering agent, and excipients, as well as the amounts of each one, one of skill in the art would be able to determine the best combination of flavors to provide the optimally flavored product for consumer demand and compliance. See, *e.g.*, Roy *et al.*, Modifying Bitterness: Mechanism, Ingredients, and Applications (1997).

In one embodiment, one or more flavoring agents are mixed with the taste-masking material prior to microencapsulating the proton pump inhibitor and, as such, are part of the taste-masking material. In other embodiments, the flavoring agent is mixed with the non-compatible excipients during the formulation process and is therefore not in contact with the proton pump inhibitor, and not part of the microencapsulation material. In another embodiment, a buffering agent, such as sodium bicarbonate, is also microencapsulated with one or more taste-masking materials.

In another embodiment, the weight fraction of the taste masking material is, *e.g.*, about 98% or less, about 95% or less, about 90% or less, about 85% or less, about 80% or less, about 75% or less, about 70% or less, about 65% or less, about 60% or less, about 55% or less, about 50% or less, about 45% or less, about 40% or less, about 35% or less, about 30% or less, about 25% or less, about 20% or less, about 15% or less, about 10% or less, about 5% or less, about 2%, or about 1% or less of the total weight of the pharmaceutical composition.

In other embodiments of the present invention, the amount of flavoring agent necessary to create a palatable product, as compared to a pharmaceutical composition comprising non-microencapulated proton pump inhibitor, is decreased by 5% or less, or by 5% to 10%, or by 10% to 20%, or by 20% to 30%, or by 30% to 40%, or by 40% to 50%, or by 50% to 60%, or by 60% to 70%, or by 70% to 80%, or by 80% to 90%, or by 90% to 95%, or by greater than 95%. In still other embodiments, no flavoring agent is necessary to create a

more palatable pharmaceutical composition as compared to a similar pharmaceutical composition comprising non-microencapulated proton pump inhibitor.

In various embodiments of the invention, the total amount of flavoring agent present in the pharmaceutical composition is less than 20 grams, or less than 15 grams, or less than 10 grams, or less than 8 grams, or less than 5 grams, or less than 4 grams, or less than 3.5 grams, or less than 3 grams, or less than 2.5 grams or less than 2 grams, or less than 1.5 grams, or less than 1 gram, or less than 500 mg, or less than 250 mg, or less than 150 mg, or less than 100 mg, or less than 50 mg.

METHODS OF MICROENCAPSULATION

The proton pump inhibitor, buffering agent and/or sleep aid may be microencapsulated by methods known by one of ordinary skill in the art. Such known methods include, *e.g.*, spray drying processes, spinning disk-solvent processes, hot melt processes, spray chilling methods, fluidized bed, electrostatic deposition, centrifugal extrusion, rotational suspension separation, polymerization at liquid-gas or solid-gas interface, pressure extrusion, or spraying solvent extraction bath. In addition to these, several chemical techniques, *e.g.*, complex coacervation, solvent evaporation, polymer-polymer incompatibility, interfacial polymerization in liquid media, in situ polymerization, in-liquid drying, and desolvation in liquid media could also be used.

The spinning disk method allows for: 1) an increased production rate due to higher feed rates and use of higher solids loading in feed solution, 2) the production of more spherical particles, 3) the production of a more even coating, and 4) limited clogging of the spray nozzle during the process.

Spray drying is often more readily available for scale-up. In various embodiments, the material used in the spray-dry encapsulation process is emulsified or dispersed into the core material in a concentrated form, *e.g.*, 10-60 % solids. The microencapsulation material is, in one embodiment, is emulsified untile about 1 to 3 μm droplets are obtained. Once a dispersion of proton pump inhibitor and encapsulation material are obtained, the emulstion is fed as droplets into the heated chamber of the pray drier. In some embodiments, the droplets are sprayed into the chamber or spun off a rotating disk. The microspheres are then dried in the heated chamber and fall to the bottom of the spray drying chamber where they are harvested.

In some embodiments of the present invention, the micropheres have irregular geometries. In other embodiments, the microspheres are aggregates of smaller particles.

In various embodiments, the proton pump inhibitor is present in the microspheres in an amount greater than 1%, greater than 2.5%, greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 25%, greater than 30%, greater than 35%, greater than 40%, greater than 45%, greater than 50%, greater than 55%, greater than 60%, greater than 65%, greater than 70%, greater than 75%, greater than 80%, greater than 85%, greater than 90 % greater than 95% or greater than 98% weight percent of the proton pump inhibitor to the microencapsulation material used to enhance the stability of the pharmaceutical composition or the taste-masking material.

COATINGS

In accordance with another aspect of the present invention, all or part of the proton pump inhibitor, buffering agent and/or sleep aid may be coated. In various embodiments contemplated by the present invention, the coating is, for example, a gastric resistant coating such as an enteric coating, a controlled-release coating, an enzymatic-controlled coating, a film coating, a sustained-release coating, an immediate-release coating, a delayed-release coating, or a moisture barrier coating. *See, e.g, Remington's Pharmaceutical Sciences*, 20th Edition (2000).

In accordance with another aspect of the invention, the coating is an enteric coating. Suitable enteric coating materials include, but are not limited to, polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate, phthalate, cellulose hydrogen phthalate, cellulose proprionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose succinate, and acrylic acid polymers and copolymers such as those formed from methyl acrylate, theyl acrylate, methyl methacrylate and/or ehtyl methacrylate with copolymers of acrylic and methacrylic acid esters (*e.g.*, Eudragit NE, Eudragit RL, Eudragit RS). In accordance with one aspect of the present invention, all or part of the proton pump inhibitor may be coated. In various embodiments contemplated by the present invention, the proton pump inhibitor is coated with, for example, a gastric resistant coating such as an enteric coating, a controlled-release coating, an enzymatic-controlled coating, a film coating, a sustained-release coating, an immediate-release coating, a delayed-release coating, or a moisture barrier coating. *See, e.g, Remington's Pharmaceutical Sciences*, 20th Edition (2000).

In accordance with another aspect of the invention, either the proton pump inhibiting agent or the sleep aid is coated. In other aspectes of the invention, some or all of the proton

pump inhibitor and some or all of the sleep aid are coated. In accordance with another aspect of the invention, the dosage form (such as a tablet, caplet, or capsule) is coated to aid swallowing. The proton pump inhibiting agent may be coated with the same material as used to coat the sleep aid or a different material. Additionally, the coating used to coat the whole dosage form (such as a film coating) may be the same as or different from the coating used to coat the proton pump inhibiting agent and/or the sleep aid.

Pharmaceutical compositions having multisite absorption profiles of the proton pump inhibitor are provided herein. In accordance with one aspect of the invention, some of the proton pump inhibitor is formulated for immediate release and some of the part of the proton pump inhibitor is formulated for delayed release. In accordance with one aspect of the invention, the delayed release coating is an enteric coating. In accordance with another aspect of the invention, the proton pump inhibitor is coated with a thin enteric coating.

Also provided herein are pharmaceutical compositions having multisite absorption profiles of the sleep aid. In accordance with one aspect of the invention, some of the sleep aid is formulated for immediate release and some of the part of the sleep aid is formulated for delayed release. In accordance with one aspect of the invention, the delayed release coating is an enteric coating. In accordance with another aspect of the invention, the sleep aid is coated with a thin enteric coating.

DOSAGE

The pharmaceutical compositions of the present invention comprising a proton pump inhibiting agent and a sleep aid are administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. In human therapy, it is important to provide a dosage form that delivers the required therapeutic amount of the each therapeutic agent in vivo, and renders therapeutic agent bioavailable in a rapid manner.

Proton Pump Inhibiting Agents

The proton pump inhibiting agent is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. In human therapy, it is important to provide a dosage form that delivers the required therapeutic amount of the drug in vivo, and renders the drug bioavailable in a rapid manner. In addition to the dosage forms described herein, the dosage

forms described by Phillips *et al.* in U.S. Patent No. 6,489,346 are incorporated herein by reference.

The percent of intact drug that is absorbed into the bloodstream is not narrowly critical, as long as a therapeutic-disorder-effective amount, *e.g.*, a gastrointestinal-disorder-effective amount of a proton pump inhibiting agent, is absorbed following administration of the pharmaceutical composition to a subject. Gastrointestinal-disorder-effective amounts in tablets may be found in U.S. Patent No. 5,622,719. It is understood that the amount of proton pump inhibiting agent and/or buffering agent that is administered to a subject is dependent on, *e.g.*, the sex, general health, diet, and/or body weight of the subject.

Illustratively, administration of a substituted bicyclic aryl-imidazole to a young child or a small animal, such as a dog, a relatively low amount of the proton pump inhibitor, *e.g.*, about 1 mg to about 30 mg, will often provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal, such as a horse, achievement of a therapeutically effective blood serum concentration will require larger dosage units, *e.g.*, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 80 mg, or about 120 mg dose for an adult human, or about 150 mg, or about 200 mg, or about 400 mg, or about 800 mg, or about 1000 mg dose, or about 1500 mg dose, or about 2000 mg dose, or about 2500 mg dose, or about 3000 mg dose or about 3200 mg dose or about 3500 mg dose for an adult horse.

In various other embodiments of the present invention, the amount of proton pump inhibitor administered to a subject is, *e.g.*, about 0.5-2 mg/Kg of body weight, or about 0.5 mg/Kg of body weight, or about 1 mg/Kg of body weight, or about 1.5 mg/Kg of body weight, or about 2 mg/Kg of body weight.

Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro and/or in vivo tests initially can provide useful guidance on the proper doses for subject administration. Studies in animal models generally may be used for guidance regarding effective dosages for treatment of gastrointestinal disorders or diseases in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route chosen for administration, the condition of the particular subject.

In various embodiments, unit dosage forms for humans contain about 1 mg to about 120 mg, or about 1 mg, or about 5 mg, or about 10 mg, or about 15 mg, or about 20 mg, or about 30 mg, or about 40 mg, or about 50 mg, or about 60 mg, or about 70 mg, or about 80,

mg, or about 90 mg, or about 100 mg, or about 110 mg, or about 120 mg of a proton pump inhibitor.

In a further embodiment of the present invention, the pharmaceutical composition is administered in an amount to achieve a measurable serum concentration of a non-acid degraded proton pump inhibiting agent greater than about 0.1 μg/ml within about 30 minutes after administration of the pharmaceutical composition. In another embodiment of the present invention, the pharmaceutical composition is administered to the subject in an amount to achieve a measurable serum concentration of a non-acid degraded or non-acid reacted proton pump inhibiting agent greater than about 0.1 μg/ml within about 15 minutes after administration of the pharmaceutical composition. In yet another embodiment, the pharmaceutical composition is administered to the subject in an amount to achieve a measurable serum concentration of a non-acide degraded or non-acid reacted proton pump inhibiting agent greater than about 0.1 μg/ml within about 10 minutes after administration of the pharmaceutical composition.

In another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15 μg/ml within about 15 minutes and to maintain a serum concentration of the proton pump inhibiting agent of greater than about 0.15 μg/ml from about 15 minutes to about 1 hour after administration of the composition. In yet another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.25 μg/ml within about 15 minutes and to maintain a serum concentration of the proton pump inhibiting agent of greater than about 0.25 μg/ml from about 15 minutes to about 1 hour after administration of the composition. In another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.35 μg/ml within about 15 minutes and to maintain a serum concentration of the proton pump inhibiting agent of greater than about 0.35 μg/ml from about 15 minutes to about 1 hour after administration of the composition. In another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.45 μg/ml within about 15 minutes and to maintain a serum concentration of the proton pump inhibiting agent of

greater than about 0.45 μg/ml from about 15 minutes to about 1 hour after administration of the composition.

In another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15 μg/ml within about 30 minutes and to maintain a serum concentration of the proton pump inhibiting agent of greater than about 0.15 μg/ml from about 30 minutes to about 1 hour after administration of the composition. In yet another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.25 μg/ml within about 30 minutes and to maintain a serum concentration of the proton pump inhibiting agent of greater than about 0.25 μg/ml from about 30 minutes to about 1 hour after administration of the composition. In another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.35 μg/ml within about 30 minutes and to maintain a serum concentration of the proton pump inhibiting agent of greater than about 0.35 μg/ml from about 30 minutes to about 1 hour after administration of the composition. In another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.45 μg/ml within about 30 minutes and to maintain a serum concentration of the proton pump inhibiting agent of greater than about 0.45 μg/ml from about 30 minutes to about 1 hour after administration of the composition.

In still another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of a non-acid degraded or non-acid reacted proton pump inhibiting agent greater than about 0.5 μg/ml within about 1 hour after administration of the composition. In yet another embodiment of the present invention, the composition is administered to the subject in an amount to achieve a measurable serum concentration of a non-acid degraded or non-acid reacted proton pump inhibiting agent greater than about 0.3 μg/ml within about 45 minutes after administration of the composition.

Contemplated compositions of the present invention provide a therapeutic effect as proton pump inhibiting agent medications over an interval of about 5 minutes to about 24

hours after administration, enabling, for example, once-a-day, twice-a-day, three times a day, etc. administration if desired.

Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective in vivo for a period of time effective to elicit a therapeutic effect. Determination of these parameters is well within the skill of the art. These considerations are well known in the art and are described in standard textbooks.

In one embodiment of the present invention, the composition is administered to a subject in a gastrointestinal-disorder-effective amount, that is, the composition is administered in an amount that achieves a therapeutically-effective dose of a proton pump inhibiting agent in the blood serum of a subject for a period of time to elicit a desired therapeutic effect. Illustratively, in a fasting adult human (fasting for generally at least 10 hours) the composition is administered to achieve a therapeutically-effective dose of a proton pump inhibiting agent in the blood serum of a subject within about 45 minutes after administration of the composition. In another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject within about 30 minutes from the time of administration of the composition to the subject. In yet another embodiment, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject within about 20 minutes from the time of administration to the subject. In still another embodiment of the present invention, a therapeutically-effective dose of the proton pump inhibiting agent is achieved in the blood serum of a subject at about 15 minutes from the time of administration of the composition to the subject.

In further embodiments, greater than about 98%; or greater than about 95%; or greater than about 90%; or greater than about 75%; or greater than about 50% of the drug absorbed into the bloodstream is in a non-acid degraded or a non-acid reacted form.

In other embodiments, the pharmaceutical compositions provide a release profile of the proton pump inhibitor, using USP dissolution methods, whereby greater than about 50% of the proton pump inhibitor is released from the composition within about 2 hours; or greater than 50% of the proton pump inhibitor is released from the composition within about 1.5 hours; or greater than 50% of the proton pump inhibitor is released from the composition within about 1 hour after exposure to gastrointestinal fluid. In another embodiment, greater than about 60% of the proton pump inhibitor is released from the composition within about 2 hours; or greater than 60% of the proton pump inhibitor is released from the composition

within about 1.5 hours; or greater than 60% of the proton pump inhibitor is released from the composition within about 1 hour after exposure to gastrointestinal fluid. In yet another embodiment, greater than about 70% of the proton pump inhibitor is released from the composition within about 2 hours; or greater than 70% of the proton pump inhibitor is released from the composition within about 1.5 hours; or greater than 70% of the proton pump inhibitor is released from the composition within about 1 hour after exposure to gastrointestinal fluid.

Sleep Aids

The sleep aid is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. In human therapy, it is important to provide a dosage form that delivers the required therapeutic amount of the drug in vivo, and renders the drug bioavailable in a rapid manner. In addition to the dosage forms described herein, the dosage forms described by Phillips *et al.* in U.S. Patent No. 6,489,346 are incorporated herein by reference.

Effective dosages of various sleep aids are compiles in Table 1. It is readily apparent that the recommended dosages vary according to the particular sleep aid, by typically range from about 0.1 mg to 30 mg for typical benzodiazapines, 5-20 mg for typical non-benzodiazapines, and slightly more for a typical anti-histamine, 10-100 mg.

DOSAGE FORM

The pharmaceutical compositions of the present invention contain desired amounts of proton pump inhibitor, a buffering agent and a sleep aid and can be in the form of, a tablet, (including a suspension tablet, a chewable tablet, a fast-melt tablet, a bite-disintegration table, a rapid-disintegration tablet, or an effervescent tablet), a pill, a powder (including a sterile packaged powder, a dispensable powder, or an effervescent powder) a capsule (including both soft or hard capsules made from animal-derived gelatin or plant-derived HPMC) a lozenge, a sachet, a troche, pellets, granules, or aerosol. These pharmaceutical compositions of the present invention can be manufactured by conventional pharmacological techniques.

Conventional pharmacological techniques include, *e.g.*, one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. See, *e.g.*, Lachman *et al.*, *The Theory and Practice of Industrial Pharmacy* (1986). Other methods include, *e.g.*, prilling, spray drying, pan coating, melt granulation, granulation, wurster coating, tangential coating, top spraying, tableting, extruding, coacervation and the like.

In one embodiment, the proton pump inhibitor and sleep aid are microencapsulated prior to being formulated into one of the above forms. In another embodiment, the proton pump inhibitor alone is microencapsualted prior to being formulated into one of the above forms. In another embodiment, some or all of the buffering agent and sleep aid are also microencapsulated prior to being further formulated into one of the above forms. In still another embodiment, some or all of the sleep aid is also microencapsulated prior to being further formulated into one of the above forms. In still other embodiments, using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000), a film coating is provided around the pharmaceutical composition.

In other embodiments, the pharmaceutical compositions further comprise one or more additional materials such as a pharmaceutically compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, surfactant, preservative, lubricant, colorant, diluent, solubilizer, moistening agent, stabilizer, wetting agent, anti-adherent, parietal cell activator, anti-foaming agent, antioxidant, chelating agent, antifungal agent, antibacterial agent, or one or more combination thereof.

In some embodiments, parietal cell activators are administered in an amount sufficient to produce the desired stimulatory effect without causing untoward side effects to patients. In one embodiment, the parietal cell activator is administered in an amount of about 5 mg to about 2.5 grams per 20 mg dose of the proton pump inhibitor.

In other embodiments, one or more layers of the pharmaceutical formulation are plasticized. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, *e.g.*, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearol, stearate, and castor oil.

Exemplary Solid Oral Dosage Compositions

Solid oral dosage compositions, *e.g.*, tablets, chewable tablets, effervescent tablets, and capsules, are prepared by mixing the proton pump inhibitor, one or more buffering agent, a sleep aid, and pharmaceutical excipients to form a bulk blend composition. When referring to these bulk blend compositions as homogeneous, it is meant that the proton pump inhibitor, buffering agent, and sleep aid are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. The individual unit dosages may also comprise film coatings, which disintegrate upon oral ingestion or upon contact with diluent.

Compressed tablets are solid dosage forms prepared by compacting the bulk blend compositions described above. In various embodiments, compressed tablets of the present invention will comprise one or more flavoring agents. In other embodiments, the compressed tablets will comprise a film surrounding the final compressed tablet. In other embodiments, the compressed tablets comprise one or more excipients and/or flavoring agents.

A chewable tablet may be prepared by compacting bulk blend compositions, described above. In one embodiment, the chewable tablet comprises a material useful for enhancing the shelf-life of the pharmaceutical composition. In another embodiment, microencapsulated material has taste-masking properties. In various other embodiments, the chewable tablet comprises one or more flavoring agents and one or more taste-masking materials. In yet other embodiments the chewable tablet comprised both a material useful for enhancing the shelf-life of the pharmaceutical formulation and one or more flavoring agents.

In various embodiments, the microencapsulated proton pump inhibitor, buffering agent, a sleep aid, and optionally one or more excipients, are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the buffering agent and the proton pump inhibitor into the gastrointestinal fluid. When at least 50% of the pharmaceutical composition has disintegrated, the compressed mass has substantially disintegrated.

A capsule may be prepared by placing the bulk blend composition, described above, inside a capsule.

Exemplary Powder Compositions

A powder for suspension may be prepared by combining proton pump inhibitor, one or more buffering agent and a suitable sleep aid. In various embodiments, the powder may comprise one or more pharmaceutical excipients and flavors. Powder for suspension is prepared by mixing the proton pump inhibitor, one or emore buffering agetns, a sleep aid, and optional pharmaceutical excipients to form a bulk blend composition. This bulk blend is uniformly subdivided into unit dosage packaging or multi-dosage packaging units. "Uniform" means the homogeneity of the bulk blend is substantially maintained during the packaging process.

In some embodiments, the proton pump inhibitor is micronized. Additional embodiments of the present invention also comprise a suspending agent and/or a wetting agent.

Effervescent powders are also prepared in accordance with the present invention. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and/or tartaric acid. When salts of the present invention are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence." Examples of effervescent salts include the following ingredients: sodium bicarbonate or a mixture of sodium bicarbonate and sodium carbonate, citric acid and/or tartaric acid. Any acid-base combination that results in the liberation of carbon dioxide can be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use and result in a pH of about 6.0 or higher.

The method of preparation of the effervescent granules of the present invention employs three basic processes: wet granulation, dry granulation and fusion. The fusion method is used for the preparation of most commercial effervescent powders. It should be noted that, although these methods are intended for the preparation of granules, the formulations of effervescent salts of the present invention could also be prepared as tablets, according to known technology for tablet preparation.

Wet granulation is one the oldest methods of granule preparation. The individual steps in the wet granulation process of tablet preparation include milling and sieving of the ingredients, dry powder mixing, wet massing, granulation, and final grinding. In various embodiments, the microencapsulated PPI is added to the other excipients of the pharmaceutical composition after they have been wet granulated.

Dry granulation involves compressing a powder mixture into a rough tablet or "slug" on a heavy-duty rotary tablet press. The slugs are then broken up into granular particles by a grinding operation, usually by passage through an oscillation granulator. The individual steps include mixing of the powders, compressing (slugging) and grinding (slug reduction or granulation). No wet binder or moisture is involved in any of the steps. In some embodiments, the microencapsulated PPI is dry granulated with other excipients in the pharmaceutical composition. In other embodiments, the microencapsulated omeprazole is added to other excipients of the pharmaceutical composition after they have been dry granulated.

Powder for Suspension

Compositions are provided comprising a pharmaceutical composition comprising at least one proton pump inhibitor, at least one buffering agent, at least one sleep aid, and at least one suspending agent for oral administration to a subject. The composition may be a powder for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

A suspension is "substantially uniform" when it is mostly homogenous, that is, when the suspension is composed of approximately the same concentration of proton pump inhibitor at any point throughout the suspension. A suspension is determined to be composed of approximately the same concentration of proton pump inhibitor throughout the suspension when there is less than about 20%, less than about 15%, less than about 13%, less than about 11%, less than about 10%, less than about 8%, less than about 5%, or less than about 3% variation in concentration among samples taken from various points in the suspension.

The concentration at various points throughout the suspension can be determined by any suitable means known in the art. For example, one suitable method of determining concentration at various points involves dividing the suspension into three substantially equal sections: top, middle and bottom. The layers are divided starting at the top of the suspension and ending at the bottom of the suspension. Any number of sections suitable for determining the uniformity of the suspension can be used, such as for example, two sections, three sections, four sections, five sections, or six or more sections. The sections can be named in any appropriate manner, such as relating to their location (e.g., top, middle, bottom), numbered (e.g., one, two, three, four, five, six, etc.), or lettered (e.g., A, B, C, D, E, F, G, etc.). The sections can be divided in any suitable configuration. In one embodiment, the sections are divided from top to bottom, which allows a comparison of sections from the top and sections from the bottom in order to determine whether and at what rate the proton pump inhibitor is settling into the bottom sections. Any number of the assigned sections suitable for determining uniformity of the suspension can be evaluated, such as, e.g., all sections, 90% of the sections, 75% of the sections, 50% of the sections, or any other suitable number of sections.

In an alternate aspect of the present invention, the suspension is substantially uniform if it comprises at least one of (a) at least about 80% label claim of proton pump inhibitor in top, middle and bottom sections determined by separating the suspension into three substantially equal sections from top to bottom for at least about 60 minutes after admixture

with water, or (b) less than about 15% variation in % label claim among each of the top, middle and bottom sections for at least about sixty minutes after admixture with water.

In some embodiments, the composition will remain substantially uniform for a suitable amount of time corresponding to the intended use of the composition, such as, e.g., for at least about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes (1 hour), about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes (2 hours), about 150 minutes, about 180 minutes (3 hours), about 210 minutes, about 4 hours, about 5 hours or more after admixture with water. In one embodiment, the suspension remains substantially uniform from about 5 minutes to about 4 hours after admixture with water. In another embodiment, the suspension remains substantially uniform from about 15 minutes to about 3 hours after admixture with water. In yet another embodiment, the suspension is remains substantially uniform from at least about 1 to at least about 3 hours after admixture with water.

In one embodiment of the present invention, the composition will remain substantially uniform at least until the suspension is prepared for administration to the patient. The suspension can be prepared for administration to the patient at any time after admixture as long as the suspension remains substantially uniform. In another embodiment, the suspension is prepared for administration to the patient from any time after admixture until the suspension is no longer uniform. For example, the suspension can be prepared for administration to the patient from about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes (1 hour), about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes (2 hours), about 150 minutes, about 180 minutes (3 hours), about 210 minutes, about 4 hours, about 5 hours or more after admixture with water. In one embodiment, the suspension is prepared for administration to the patient from about 5 minutes to about 4 hours after admixture. In another embodiment, the suspension is prepared for administration to the patient from about 15 minutes to about 3 hours after admixture. In yet another embodiment, the suspension is prepared for administration to the patient from at least about 1 to at least about 3 hours after admixture.

In an alternate embodiment, the composition remains substantially uniform until the composition is actually administered to the patient. The suspension can be administered to the patient at any time after admixture as long as the suspension remains substantially uniform. In one embodiment, the suspension is administered to the patient from any time after admixture until the suspension is no longer uniform. For example, the suspension can

be administered to the patient from about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes (1 hour), about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes (2 hours), about 150 minutes, about 180 minutes (3 hours), about 210 minutes, about 4 hours, about 5 hours or more after admixture with water. In one embodiment, the suspension is administered to the patient from about 5 minutes to about 4 hours after admixture. In another embodiment, the suspension is administered to the patient from about 15 minutes to about 3 hours after admixture. In yet another embodiment, the suspension is administered to the patient from at least about 1 to at least about 3 hours after admixture.

In one embodiment, the composition comprises at least one proton pump inhibitor, at least one buffering agent, at least one sleep aid, and xanthan gum. The composition is a powder for suspension, and upon admixture with water, a first suspension is obtained that is substantially more uniform when compared to a second suspension comprising the proton pump inhibitor, the buffering agent, the sleep aid, and suspending agent, wherein the suspending agent is not xanthan gum. In one embodiment, the first suspension comprises at least one of (a) at least about 87% label claim of proton pump inhibitor in top, middle and bottom sections determined by separating the suspension into three substantially equal sections from top to bottom for at least about five minutes after admixture with water, or (b) less than about 11% variation in % label claim among each of the top, middle and bottom sections for at least about five minutes after admixture with water.

Other Exemplary Compositions

Pharmaceutical compositions suitable for buccal or sublingual administration include intra-oral batch or solid dosage forms, *e.g.*, lozenges. Other types of release delivery systems are available and known to those of skill in the art. Examples of such delivery systems include, but are not limitd to: polymer-based systems such as polylactic acid, polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer-based systems that are lipids, including sterols such as cholesterol, cholesterol esters and fatty acids, or neutral fats, such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings; compressed tablets using conventional binders and excipients partially fused implants and the like. See, *e.g.*, Liberman *et al.*, *Pharmaceutical Dosage Forms*, 2 Ed., Vol. 1, pp. 209-214 (1990).

For the sake of brevity, all patents and other references cited herein are incorporated by reference in their entirety.

EXAMPLES

The present invention is further illustrated by the following examples, which should not be construed as limiting in any way. The experimental procedures to generate the data shown are discussed in more detail below. For all formulations herein, multiple doses may be proportionally compounded as is known in the art. The coatings, layers and encapsulations are applied in conventional ways using equipment customary for these purposes.

The invention has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation.

Example 1 Spinning Disk Microencapsulation Process

The basic operation for the spinning disk-solvent process used is as follows: An encapsulation solution is prepared by dissolving the encapsulation material in the appropriate solvent. Proton pump inhibitor (PPI) in combination with an antacid and a sleep aid, or alone if intended to be microencapsulated and then combined with an antacid and a sleep aid, is dispersed in the coating solution and fed onto the center of the spinning disk. A thin film is produced across the surface of the disk and atomization occurs as the coating material left the periphery of the disk. The microspheres are formed by removal of the solvent using heated airflow inside the atomization chamber and collected as a free-flowing powder using a cyclone separator.

Example 2. Spray Drying Microencapsulation Process

A spray dryer consists of the same components as a spinning disk except atomization is achieved through an air nozzle instead of a spinning disk.

Example 3: Preparation of Powder for Suspension for Oral Dosing

Powder for suspension (liquid oral pharmaceutical composition) according to the present invention, is prepared by mixing PPI (40 mg omeprazole in the form of enteric-coated granules, microencapsulated omeprazole, or omeprazole base) with at least one buffering agent and a sleep aid. In one embodiment, omeprazole or other proton pump inhibitor, which can be obtained from powder, capsules, and tablets or obtained from the solution for parenteral administration, is mixed with sodium bicarbonate (1680 mg), sleep aid, and sweeteners and flavors.

Example 4: Capsule Formulations

The following specific formulations are provided by way of reference only and are not intended to limit the scope of the invention. Each formulation contains therapeutically effective doses of PPI and sleep aid as well as sufficient buffering agent to prevent acid

degradation of at least some of the PPI by raising the pH of gastric fluid. Amounts of buffer are expressed in weight as well as in molar equivalents (mEq). Amounts of sleep aid are typically expressed in a per unit dose amount. The capsules are prepared by blending the PPI and sleep aid with buffering agents, and homogeneously blending with excipients as shown in Tables 4.A. to 4.F. below. The appropriate weight of bulk blend composition is filled into a hard gelatine capsule (size 00) using an automatic encapsualtor (H & K 1500 or MG2 G60).

4.A. Omeprazole (20 mg)-Triazolam Capsule

PPI	Buffering Agent	Sleep Aid	Excipient
20 mg omeprazole per capsule	20.6 mEq or 600 mg $Mg(OH)_2$ 3.0 mEq or 250 mg $NaHCO_3$ 23.6 mEq or 850 mg total buffer	0.125 mg triazolam per capsule	50 mg Ac-Di-Sol 50 mg Klucel 10 mg magnesium stearate

4.B. Ompeprazole (40 mg)-Zolpidem Capsule

PPI	Buffering Agent	Sleep Aid	Excipient
40 mg omeprazole per capsule	17.1 mEq or 500 mg $Mg(OH)_2$ 4.2 mEq or 350 mg $NaHCO_3$ 24.8 mEq or 850 mg total buffer	0.125 mg zolpidem per capsule	40 mg Ac-Di-Sol 45 mg Klucel 10 mg magnesium stearate

4.C. Lansoprazole (15 mg)-Zaleprone Capsule

PPI	Buffering Agent	Sleep Aid	Excipient
15 mg lansoprazole per capsule	17.1 mEq or 500 mg $Mg(OH)_2$ 3.0 mEq or 250 mg $NaHCO_3$ 20.7 mEq or 750 mg total buffer	5 mg zaleprone per capsule	30 mg Ac-Di-Sol 15 mg Klucel 7 mg magnesium stearate

4.D. Lansoprazole (30 mg)-Diphenhydramine Capsule

PPI	Buffering Agent	Sleep Aid	Excipient
30 mg lansoprazole per capsule	20.6 mEq or 600 mg $Mg(OH)_2$ 4.2 mEq or 350 mg $NaHCO_3$	25 mg diphenhydramine per capsule	20 mg Ac-Di-Sol 30 mg Klucel 10 mg magnesium stearate

	24.8 mEq or 950 mg total buffer		

4.E. Omeprazole (60 mg)-Triazolam Capsule

PPI	Buffering Agent	Sleep Aid	Excipient
60 mg ompeprazole per capsule	20.6 mEq or 600 mg $Mg(OH)_2$ 3.0 mEq or 250 mg $NaHCO_3$ 23.6 mEq or 850 mg total buffer	0.125 mg triazolam per capsule	20 mg Ac-Di-Sol 25 mg Klucel 10 mg magnesium stearate

4.F. Omeprazole (60 mg)-Zaleprone Capsule

PPI	Buffering Agent	Sleep Aid	Excipient
60 mg ompeprazole per capsule	17.1 mEq or 500 mg $Mg(OH)_2$ 3.0 mEq or 250 mg $NaHCO_3$ 20.1 mEq or 750 mg total buffer	5 mg zaleprone per capsule	30 mg Ac-Di-Sol 15 mg Klucel 7 mg magnesium stearate

Example 5: Tablet Formulations

The following specific formulations are provided by way of reference only and are not intended to limit the scope of the invention. Each formulation contains therapeutically effective doses of PPI and sleep aid as well as sufficient buffering agent to prevent acid degradation of at least some of the PPI by raising the pH of gastric fluid. Amounts of buffer are expressed in weight as well as in molar equivalents (mEq). Amounts of sleep aid are typically expressed in a per unit dose amount. The tablets are prepared by blending the PPI and sleep aid with buffering agents, and homogeneously blending with excipients as shown in Tables 5.A. to 5.F. below. The appropriate weight of bulk blended composition is compressed using ½-inch FFBE toolings in a rotary press (Manesty Epxress) to achieve a hardness of 20-24 kPa.

5.A. Ompeprazole (20 mg)-Triazolam Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
20 mg omeprazole per tablet	20.6 mEq or 600 mg $Mg(OH)_2$ 3.0 mEq or 250 mg $NaHCO_3$ 23.6 mEq or 850 mg total	0.125 triazolam mg per tablet	20 mg Ac-Di-Sol 80 mg Klucel 10 mg magnesium stearate

	buffer		

5.B. Omeprazole (40 mg)-Zolpidem Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
40 mg omeprazole per tablet	17.1 mEq or 500 mg $Mg(OH)_2$ 4.2 mEq or 350 mg $NaHCO_3$ 24.8 mEq or 850 mg total buffer	5 mg zolpidem per tablet	20 mg Ac-Di-Sol 80 mg Klucel 10 mg magnesium stearate

5.C. Lansoprazole (15 mg)-Zaleprone Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
15 mg lansoprazole per tablet	17.1 mEq or 500 mg $Mg(OH)_2$ 3.0 mEq or 250 mg $NaHCO_3$ 20.1 mEq or 750 mg total buffer	5 mg zaleprone per tablet	20 mg Ac-Di-Sol 80 mg Klucel 10 mg magnesium stearate

5.D. Lansoprazole (30 mg)-Diphenhydramine Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
30 mg lansoprazole per tablet	20.6 mEq or 500 mg $Mg(OH)_2$ 4.2 mEq or 350 mg $NaHCO_3$ 24.8 mEq or 850 mg total buffer	25 mg diphenhydramine per tablet	20 mg Ac-Di-Sol 80 mg Klucel 10 mg magnesium stearate

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5.E. Omeprazole (60 mg)-Triazolam Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
60 mg omeprazole per tablet	20.6 mEq or 600 mg $Mg(OH)_2$ 3.0 mEq or 250 mg $NaHCO_3$ 23.6 mEq or 850 mg total buffer	0.125 mg triazolam per tablet	20 mg Ac-Di-Sol 80 mg Klucel 10 mg magnesium stearate

5.F. Omeprazole (60 mg)-Zaleprone Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
60 mg omprazole per tablet	17.1 mEq or 500 mg $Mg(OH)_2$ 3.0 mEq or 250 mg	5 mg zaleprone per tablet	20 mg Ac-Di-Sol 80 mg Klucel 10 mg magnesium

	$NaHCO_3$ 20.1 mEq or 850 mg total buffer		stearate

Example 6: Chewable Tablet Formulations

The following specific formulations are provided by way of reference only and are not intended to limit the scope of the invention. Each formulation contains therapeutically effective doses of PPI and sleep aid as well as sufficient buffering agent to prevent acid degradation of at least some of the PPI by raising the pH of gastric fluid. Amounts of buffer are expressed in weight as well as in molar equivalents (mEq). Amounts of sleep aid are typically expressed in a per unit dose amount. The tablets are prepared by blending the PPI and sleep aid with buffering agents, and homogeneously blending with excipients as shown in Tables 6.A to 6.F. below. The appropriate weight of bulk blended composition is compressed using 5/8-inch FFBE toolings in a rotary press (Manesty Epxress) to achieve a hardness of 17-20 kPa.

6.A. Ompeprazole (20 mg)-Triazolam Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
20 mg per tablet (microencapsulated)	20.6 mEq or 600 mg $Mg(OH)_2$ 5.0 mEq or 420 mg $NaHCO_3$ 25.6 mEq or 1020 mg total buffer	0.125 triazolam mg per tablet	170 mg Xylitab 30 mg Ac-Di-Sol 100 mg Klucel 25 mg cherry flavor 15 mg magnesium stearate 3 mg Red #40 Lake

6.B. Omeprazole (40 mg)-Zolpidem Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
40 mg per tablet (microencapsulated)	23.7 mEq or 700 mg $Mg(OH)_2$ 7.2 mEq or 600 mg $NaHCO_3$ 30.9 mEq or 1300 mg total buffer	5 mg zolpidem per tablet	170 mg Dipac sugar 30 mg Ac-Di-Sol 120 mg Klucel 27 mg grape flavor 15 mg magnesium stearate 1 mg Red #40 Lake 1 mg Blue #2 Lake

6.C. Lansoprazole (15 mg)-Zaleprone Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
15 mg lansoprazole per tablet	23.7 mEq or 500 mg $Mg(OH)_2$ 10.0 mEq or 250 mg	5 mg zaleprone per tablet	170 mg Dipac sugar 30 mg Ac-Di-Sol 120 mg Klucel

	$NaHCO_3$ 33.7 mEq or 140 mg total buffer		27 mg grape flavor 15 mg magnesium stearate 1 mg red #40 lake 1 mg blue #2 lake

6.D. Lansoprazole (30 mg)-Diphenhydramine Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
30 mg lansoprazole per tablet (microencapsulated)	23.7 mEq or 700 mg $Mg(OH)_2$ 5 mEq or 420 mg $NaHCO_3$ 28.7 mEq or 1020 mg total buffer	25 mg diphenhydramine per tablet	170 mg Xylitab 30 mg Ac-Di-Sol 100 mg Klucel 25 mg cherry flavor 15 mg magnesium stearate 3 mg Red #40 Lake

6.E. Omeprazole (60 mg)-Triazolam Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
60 mg omeprazole per tablet	15 mEq or 750 mg $Ca(OH)_2$ 15 mEq or 1260 mg $NaHCO_3$ 30 mEq or 2010 mg total buffer	0.125 mg triazolam per tablet	170 mg Xylitab 30 mg Ac-Di-Sol 100 mg Klucel 25 mg cherry flavor 15 mg magnesium stearate 3 mg Red #40 Lake

6.F. Omeprazole (60 mg)-Zaleprone Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
60 mg omprazole per tablet	15 mEq or 750 mg $Ca(OH)_2$ 10 mEq or 840 mg $NaHCO_3$ 25 mEq or 1590 mg total buffer	5 mg zaleprone per tablet	170 mg Xylitab 30 mg Ac-Di-Sol 100 mg Klucel 15 mg mint flavor 15 mg magnesium stearate

Example 7: Bite-Disintegration Chewable Tablet Formulations

The following specific formulations are provided by way of reference only and are not intended to limit the scope of the invention. Each formulation contains therapeutically effective doses of PPI and sleep aid as well as sufficient buffering agent to prevent acid degradation of at least some of the PPI by raising the pH of gastric fluid. Amounts of buffer are expressed in weight as well as in molar equivalents (mEq). Amounts of sleep aid are typically expressed in a per unit dose amount. The tablets are prepared by blending the PPI and sleep aid with buffering agents, and homogeneously blending with excipients as shown in Tables 7.A to 7.F. below. The appropriate weight of bulk blended composition is compressed

using 5/8-inch FFBE toolings in a rotary press (Manesty Epxress) to achieve a hardness of 8-12 kPa.

7.A. Ompeprazole (20 mg)-Triazolam Bite-Disintegration Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
20 mg per tablet	20.6 mEq or 600 mg $Mg(OH)_2$ 5.0 mEq or 420 mg $NaHCO_3$ 25.6 mEq or 1020 mg total buffer	0.125 triazolam mg per tablet	60 mg sucralose 60 mg Ac-Di-Sol 60 mg pregelatinized starch 30 mg Klucel 25 mg cherry flavor 15 mg magnesium stearate 3 mg Red #40 Lake

7.B. Omeprazole (40 mg)-Zolpidem Bite-Disintegration Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
40 mg omeprazole per tablet	23.7 mEq or 700 mg $Mg(OH)_2$ 7.2 mEq or 600 mg $NaHCO_3$ 30.9 mEq or 1300 mg total buffer	5 mg zolpidem per tablet	60 mg sucralose 60 mg Ac-Di-Sol 60 mg pregelatinized starch 30 mg Klucel 27 mg grape flavor 15 mg magnesium stearate 1 mg Red #40 Lake 1 mg Blue #2 Lake

7.C. Lansoprazole (15 mg)-Zaleprone Bite-Disintegration Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
15 mg lansoprazole per tablet	23.7 mEq or 500 mg $Mg(OH)_2$ 7.2 mEq or 600 mg $NaHCO_3$ 33.7 mEq or 1540 mg total buffer	5 mg zaleprone per tablet	60 mg sucralose 70 mg Ac-Di-Sol 70 mg pregelatinized starch 30 mg Klucel 27 mg grape flavor 15 mg magnesium stearate 1 mg Red #40 Lake 1 mg Blue #2 lake

7.D. Lansoprazole (30 mg)-Diphenhydramine Bite-Disintegration Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
30 mg lansoprazole per tablet	23.7 mEq or 700 mg $Mg(OH)_2$ 5 mEq or 420 mg	25 mg diphenhydramine per tablet	60 mg sucralose 60 mg Ac-Di-Sol 70 mg pregelatinized

	$NaHCO_3$ 28.7 mEq or 1020 mg total buffer		starch 30 mg Klucel 25 mg cherry flavor 15 mg magnesium stearate 3 mg Red #40 Lake

7.E. Omeprazole (60 mg)-Triazolam Bite-Disintegration Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
60 mg omeprazole per tablet	15 mEq or 750 mg $Ca(OH)_2$ 15 mEq or 1260 mg $NaHCO_3$ 30 mEq or 2010 mg total buffer	0.125 mg triazolam per tablet	60 mg sucralose 60 mg Ac-Di-Sol 60 mg pregelatinized starch 30 mg Klucel 25 mg cherry flavor 15 mg magnesium stearate 3 mg Red #40 Lake

7.F. Omeprazole (60 mg)-Zaleprone Bite-Disintegration Chewable Tablet

PPI	Buffering Agent	Sleep Aid	Excipient
60 mg omprazole per tablet	15 mEq or 750 mg $Ca(OH)_2$ 10 mEq or 840 mg $NaHCO_3$ 25 mEq or 1590 mg total buffer	5 mg zaleprone per tablet	60 mg sucralose 60 mg Ac-Di-Sol 60 mg pregelatinized starch 30 mg Klucel 15 mg mint flavor 15 mg magnesium stearate

Example 8: Combination Tablet Delivering Bolus And Time-Released Doses of PPI

Tablets may be compounded using known methods by forming an inner core of 10 mg omeprazole powder, mixed with 750 mg sodium bicarbonate, and an outer core of 5-200 mg omeprazole enteric-coated granules and a therapeutically effective amount of a sleep aid mixed with known binders and excipients. Upon ingestion of the whole tablet, the tablet dissolves and the inner core is dispersed in the stomach where it is absorbed for immediate therapeutic effect. The enteric-coated granules are later absorbed in the duodenum to provide symptomatic relief later in the dosing cycle. This tablet is particularly useful in patients who experience breakthrough gastritis between conventional doses, such as while sleeping or in the early morning hours.

Example 9: Powder for Suspension Formulations

The following specific formuations are provided by way of reference only and are not intended to limit the scope of the invention. Each formulation contains therapeutically effective doses of PPI and sleep aid as well as sufficient buffering agent to prevent acid degredation of at least some of the PPI by raising the pH of gastric fluid.

Table 10.A. Omeprazole (20 mg) – Triazolam

	1	2	3	4	5	6	7	8	9	10
Omeprazole	20	20	20	20	20	20	20	20	20	20
Triazolam	0.125	0.25	0.125	0.25	0.125	0.25	0.125	0.25	0.125	0.25
Sodium Bicarbonate	1895	1680	1825	1895	1375	1650	1825	1650	1620	1600
Xylitol 300 (sweetener)	2000	2000	1500	1750	1750	2500	2000	1500	2000	2500
Sucrose-powder (sweetener)	1750	2000	2250	2000	2500	1500	1750	2500	2000	1500
Sucralose (sweetener)	125	100	150	75	100	70	80	130	125	80
Xanthan Gum	17	55	31	80	39	48	72	25	64	68
Peach Flavor	47	15	75	32	60	50	77	38	35	62
Peppermint	26	10	29	28	36	42	56	17	16	50
Total Weight	5880	5880	5880	5880	5880	5880	5880	5880	5880	5880

Table 10.B. Omeprazole (40 mg) – Zoldipem

	1	2	3	4	5	6	7	8	9	10
Omeprazole	40	40	40	40	40	40	40	40	40	40
Zoldipem	5	7.5	10	5	7.5	10	5	7.5	10	5
Sodium Bicarbonate	2010	1375	1680	1520	1400	1825	1680	1650	2030	1375
Xylitol 300 (sweetener)	1500	2750	2000	2500	2000	1750	2000	2500	1500	1750
Sucrose-powder (sweetener)	2000	1500	2000	1500	2250	2000	2000	1500	2000	2500
Sucralose (sweetener)	150	100	75	125	100	95	80	80	130	125
Xanthan Gum 75	74	22	45	80	17	58	39	40	64	33
Peach Flavor	64	80	28	76	55	68	30	35	82	32
Peppermint	42	13	12	39	18	44	11	35	34	25
Total Weight	5880	5880	5880	5880	5880	5880	5880	5880	5880	5880

Table 10.C. Omeprazole (60 mg) – Zaleplon

	1	2	3	4	5	6	7	8	9	10

Omeprazole	60	60	60	60	60	60	60	60	60	60
Zaleplon	5	10	15	20	5	10	15	20	5	10
Sodium Bicarbonate	1750	2475	1310	2130	2005	1580	1110	2300	1325	140(
Xylitol 300 (sweetener)	2000	1500	2000	1500	2000	2500	2250	1500	1750	250(
Sucrose-powder (sweetener)	1750	1500	2250	2000	1500	1500	2250	1750	2500	175(
Sucralose (sweetener)	145	130	75	70	150	150	60	100	80	75
Xanthan Gum 75	15	57	22	19	64	39	33	29	44	50
Peach Flavor	92	105	87	78	57	31	69	95	88	25
Peppermint	68	53	76	23	44	20	48	46	33	20
Total Weight	5880	5880	5880	5880	5880	5880	5880	5880	5880	588(

Example 10: Combination therapy for sleep-onset insomnia and GERD

For a combined treatment when a patient experiences both GERD and the inability to fall asleep, a formulation of the present invention is administered for relief of both the gastric acid disorder and sleepless. Administration of a therapeutic amount of buffered, non-enteric-coated PPI, formulated for rapid uptake via stomach delivery, in combination with a therapeutically effective amount of a fast-acting sleep aid, gives rapid relief from gastric acid pain and induces sleep. Treatment may be delivered via a chewable tablet, a suspension tablet, an effervescent tablet, a rapid dissolving tablet, or various liquid formulations and aqueous suspensions. Typical dosing is as follows: 20-40 mg PPI (omeprazole); 0.125 mg triazolam or alternatively, 5 mg zolipidem; and 750-1500 mg buffering agent. Effective amounts of other sleep aids are found in Table 1.

For a combined treatment when a subject experiences an episode of GERD that awakens the subject, a formulation of the present invention may be administered. Administration of a therapeutic amount of buffered, non-enteric-coated PPI, formulated for rapid uptake via stomach delivery, in combination with a therepeutically effective amount of a fast-acting sleep aid, provides rapid relief from gastric acid pain and re-induces sleep (induces a return to sleep). Treatment may be delivered via a chewable tablet, a suspension tablet, a rapid-disintegration tablet, or various liquid formulations and aqueous suspensions. Typical dosing is as follows: 20-40 mg PPI, *e.g.*, omeprazole; a fast-acting sleep aid, *e.g.*, 0.125 mg triazolam or 5 mg zolipidem; and 750-1500 mg buffering agent. Effective amounts of other sleep aids are found in Table 1.

To prevent sleeplessness when a subject would otherwise experience an episode of nocturnal GERD that would awaken the subject, a formulation of the present invention may

be administered. Administration of a therapeutic amount of enteric-coated buffered PPI along in combination with a therapeutically effective amount of a long-acting sleep aid prior to retiring prevents the subject from experiencing an episode of GERD during the night, and also prevents awakening (induces sleep maintenance). Treament is delivered via a capsule or enterically coated tablet. Typical dosing is as follows 20-40 mg coated PPI, *e.g.*, omeprazole); a long-acting sleep aid, *e.g.*, 7.5-30 mg temazapem; and 750 to 1500 mg buffering agent. Effective amounts of other sleep aids are found in Table 1.

Modifications, equivalents, and variations of the present invention are possible in light of the teachings above, such that the invention may be embodied in other forms without departing from the spirit or essential characterics of the invention. The present embodiments are therefore to be considered as illustrative and not restrictive, the scope of the inventnion being indicated by the appended claims rather than by the foregoing description. All changes that come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of at least one acid labile proton pump inhibitor;

(b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid; and

(c) a therapeutically effective amount of at least one sleep aid.

2. The composition of Claim 1, wherein an initial serum concentration of the proton pump inhibitor is greater than about 0.1 μg/ml at any time within about 30 minutes after administration.

3. The composition of Claim 1, wherein the proton pump inhibitor selected from the group consisting of omeprazole, hydroxyomeprazole, esomeprazole, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, periprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, metabolite or prodrug thereof.

4. The composition of Claim 3, wherein the proton pump inhibitor is omeprazole or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, metabolite or prodrug thereof.

5. The composition of Claim 1 comprising about 15 mg, 20 mg, 30 mg or 40 mg of the proton pump inhibitor.

6. The composition of Claim 1, wherein an initial serum concentration of the proton pump inhibitor is greater than about 0.5 μg/ml at any time within about 1 hour after administration of the pharmaceutical composition.

7. The composition of Claim 1, wherein the composition is administered in an amount to maintain a serum concentration of the proton pump inhibitor greater than about 0.15 μg/ml from about 15 minutes to about 1 hour after administration of the composition.

8. The composition of Claim 1, wherein upon oral administration to the subject, the composition provides a pharmacokinetic profile such that at least about 50% of total area under serum concentration time curve (AUC) for the proton pump inhibitor occurs within about 2 hours after administration of a single dose of the composition to the subject.

9. The composition of Claim 1, wherein upon oral administration to the subject, the composition provides a pharmacokinetic profile such that the proton pump inhibitor reaches a maximum serum concentration within about 1 hour after administration of a single dose of the composition.

10. The composition of Claim 1, wherein the proton pump inhibitor is microencapsulated with a material that enhances the shelf-life of the pharmaceutical composition.

11. The composition of Claim 10, wherein the material that enhances the shelf-life of the pharmaceutical composition is selected from the group consisting of cellulose hydroxypropyl ethers, low-substituted hydroxypropyl ethers, cellulose hydroxypropyl methyl ethers, ethylcellulose polymers, ethylcelluloses and mixtures thereof, polyvinyl alcohol, hydroxyethylcelluloses, carboxymethylcelluloses and salts of carboxymethylcelluloses, polyvinyl alcohol and polyethylene glycol co-polymers, monoglycerides, triglycerides, polyethylene glycols, modified food starch, acrylic polymers, mixtures of acrylic polymers with cellulose ethers, cellulose acetate phthalate, sepifilms, cyclodextrins, and mixtures thereof.

12. The composition of Claim 1, wherein at least some of the proton pump inhibitor is coated.

13. The composition of claim 12, wherein the coating is selected from a gastric resistant coating, a controlled-release coating, an enzymatic-controlled coating, a film coating, a sustained-release coating, an immediate-release coating, and a delayed-release coating.

14. The composition of Claim 1, wherein the buffering agent is an alkaline metal salt or a Group IA metal selected from a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal.

15. The composition of Claim 1, wherein the buffering agent is selected from the group consisting of an amino acid, an acid salt of an amino acid, an alkali salt of an amino acid, aluminum hydroxide, aluminum hydroxide/magnesium carbonate/calcium carbonate co-precipitate, aluminum magnesium hydroxide, aluminum hydroxide/magnesium hydroxide co-precipitate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, calcium acetate, calcium bicarbonate, calcium borate, calcium carbonate, calcium citrate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium lactate, calcium phthalate, calcium phosphate, calcium succinate, calcium tartrate, dibasic sodium phosphate, dipotassium hydrogen phosphate, dipotassium phosphate, disodium hydrogen phosphate,

disodium succinate, dry aluminum hydroxide gel, L-arginine, magnesium acetate, magnesium aluminate, magnesium borate, magnesium bicarbonate, magnesium carbonate, magnesium citrate, magnesium gluconate, magnesium hydroxide, magnesium lactate, magnesium metasilicate aluminate, magnesium oxide, magnesium phthalate, magnesium phosphate, magnesium silicate, magnesium succinate, magnesium tartrate, potassium acetate, potassium carbonate, potassium bicarbonate, potassium borate, potassium citrate, potassium metaphosphate, potassium phthalate, potassium phosphate, potassium polyphosphate, potassium pyrophosphate, potassium succinate, potassium tartrate, sodium acetate, sodium bicarbonate, sodium borate, sodium carbonate, sodium citrate, sodium gluconate, sodium hydrogen phosphate, sodium hydroxide, sodium lactate, sodium phthalate, sodium phosphate, sodium polyphosphate, sodium pyrophosphate, sodium sesquicarbonate, sodium succinate, sodium tartrate, sodium tripolyphosphate, synthetic hydrotalcite, tetrapotassium pyrophosphate, tetrasodium pyrophosphate, tripotassium phosphate, trisodium phosphate, trometamol, and mixtures thereof.

16. The composition of Claim 1, wherein the buffering agent is selected from sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium oxide, magnesium hydroxide, magnesium carbonate, aluminum hydroxide, and mixtures thereof.

17. The composition of Claim 1, wherein the buffering agent is selected from sodium bicarbonate, calcium carbonate, magnesium hydroxide, and mixtures thereof.

18. The composition of Claim 1, wherein the buffering agent is present in an amount of about 0.1 mEq/mg to about 5 mEq/mg of the proton pump inhibitor.

19. The composition of Claim 1, wherein the buffering agent is present in an amount of at least about 5 mEq.

20. The composition of Claim 1, wherein the buffering agent is present in an amount of at least about 10 mEq.

21. The composition of Claim 1, wherein the buffering agent is present in an amount of about 10-40 mEq.

22. The composition of Claim 1 comprising about 200 to 3000 mg of buffering agent.

23. The composition of Claim 1 comprising about 1000 to about 2000 mg of buffering agent.

24. The composition of Claim 1, wherein the sleep aid is a hypnotic.

25. The composition of Claim 24, wherein the hypnotic is fast-acting, intermediate-acting, or long-acting.

26. The composition of Claim 24, wherein the hypnotic is a benzodiazepine hypnotic, non-benzodiazepine hypnotic, antihistamine hypnotic, antidepressant hypnotic, herbal extract, barbiturate, or peptide hypnotic.

27. The composition of Claim 24, wherein the hypnotic is a fast-acting benzodiazepine, an intermediate-acting benzodiazepine, or a long-acting benzodiazepine.

28. The composition of Claim 27, wherein the fast-acting benzodiazepine is triazolam, brotizolam, loprazolam, lormetazepam, flunitrazepam, flurazepam, nitrazepam, or quazepam.

29. The composition of Claim 27, wherein the intermediate-acting benzodiazepine is estazolam, temazepam, lorazepam, oxazepam, diazepam, halazepam, and prazepam.

30. The composition of Claim 27, wherein the long-acting benzodiazepine is alprazolam, chlordiazepoxide, or clorazepate.

31. The composition of Claim 26, wherein the non-benzodiazepine hypnotic is a an imidazopyridine or pyrazolopyrimidine hypnotic.

32. The composition of Claim 31, wherein the imidazopyridine is zolpidem or zolpidem tartarate.

33. The composition of Claim 31, wherein the pyrazolopyrimidine is zopiclone, eszopiclone, or zaleplon.

34. The composition of Claim 26, wherein the non-benzodiazepine hypnotic is indiplone.

35. The composition of Claim 26, wherein the antihistamine hypnotic is diphenhydramine, doxylamine, phenyltoloxamine, or pyrilamine.

36. The composition of Claim 26, wherein the antidepressant hypnotic is doxepin, amtriptyline, trimipramine, trazodon, nefazodone, buproprion, or bupramityiptyline.

37. The composition of Claim 26, wherein the herbal extract is a valerian extract.

39. The composition of Claim 26, wherein the peptide hypnotic is gabapeptin.

40. The composition of Claim 24, wherein the hypnotic is formulated for controlled release.

41. The composition of Claim 24, wherein the hypnotic is formulated for pulsed release.

42. The composition of Claim 1, wherein the composition is in a dosage form selected from a powder, a tablet, a bite-disintegration tablet, a chewable tablet, a capsule, a caplet, an effervescent powder, a rapid-disintegration tablet, or an aqueous suspension produced from powder.

43. The composition of Claim 1, further comprising one or more excipients selected from the group consisting of parietal cell activators, erosion facilitators, flavoring agents, sweetening agents, diffusion facilitators, antioxidants and carrier materials selected from binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, anti-adherents, and antifoaming agents.

44. A method for treating a gastric acid related disorder and inducing sleep in a subject comprising administering to the subject a pharmaceutical composition comprising:

(a) a therapeutically effective amount of at least one acid labile proton pump inhibitor;

(b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid; and

(c) a therapeutically effective amount of at least one sleep aid,

wherein the proton pump inhibitor treats the gastric acid related disorder and the sleep aid induces sleep in the subject.

45. The method of Claim 44, wherein the composition is formulated for stomach delivery of the proton pump inhibitor.

46. The method of Claim 44, wherein the gastric acid-related disorder is duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison syndrome, heartburn, esophageal disorder, or acid dyspepsia.

47. The method of Claim 44, wherein the proton pump inhibitor prevents the gastric acid related disorder when the subject is asleep.

48. The method of Claim 44 wherein the proton pump inhibitor treats the gastric acid related disorder and the sleep aid induces sleep in a subject suffering from sleeplessness or insomnia.

49. The method of Claim 48, wherein the insomnia is sleep onset insomnia, sleep maintenance insomnia, or sleep offset insomnia.

50. The method of Claim 44, wherein the sleep aid induces sleep onset in a subject suffering from sleep onset insomnia.

51. The method of Claim 44, wherein the composition is administered before the subject retires.

52. The method of Claim 44, wherein the sleep aid induces sleep maintenance in a subject suffering from sleep maintenance insomnia.

53. The method of Claim 44, wherein the sleep aid prevents awakening in a subject suffering from sleep offset insomnia.

54. The method of Claim 44, wherein the sleep aid induces sleep in a subject after the subject is awakened by distress associated with the gastric acid related disorder.

55. The method of Claim 44, wherein the composition is in a dosage form selected from a powder, a tablet, a bite-disintegration tablet, a chewable tablet, a capsule, a caplet, an effervescent powder, a rapid-disintegration tablet, or an aqueous suspension produced from powder.